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JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY NOVEMBER 25 1950

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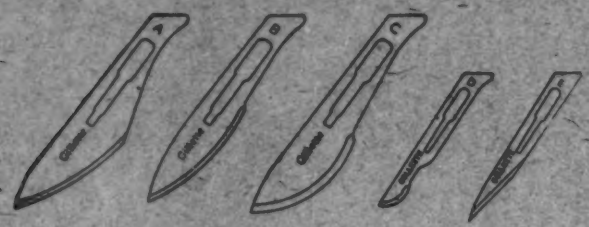

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 25 1950

SCIENTIFIC METHOD IN MEDICAL RESEARCH*

BY

Sir HENRY DALE, O.M., G.B.E., M.D., F.R.C.P., F.R.S.

It was as long ago as December, 1949, that I was honoured by an invitation to give this lecture, as an introduction to the series then being planned. "Scientific Method in Medical Research" was suggested to me as a title; and, having no alternative of my own ready to offer, I accepted the suggestion with a procrastinator's easy optimism. Only more recently did I begin to recognize that, to deal adequately with the multitudinous applications of such a theme, a variously qualified syndicate would be required—a greater company of experts, indeed, than those who are to deliver the 40-odd lectures of this series on the "Scientific Basis of Medicine." My task, however, is to offer some kind of general introduction, and not to attempt a speculative review of what the following lectures will present in detail. And I should, further, not wish to be precluded from the discussion of some of the conditions of medical research which concern rather its general direction, or its more immediate aims, than its scientific methods. I hope that I may be allowed, therefore, some freedom in interpreting the title which I accepted. "Methods and Aims in Medical Research" would perhaps more accurately indicate the scope of what I have in mind to put before you.

The Beginnings of "Modern Science"

It will be one purpose of this lecture to bring to your notice the effective and still progressive penetration of the methods and the standards of scientific research into medical thought and practice, as a remarkably recent development; and the more remarkable in that for its origin we have to go back to the very beginning of experimental science in this country. It is not without significance, I think, that the great movement which brought about the new birth, in the sixteenth and seventeenth centuries, of the method of investigating Nature by direct observation and experiment which we call "modern science" had as its pioneers in this country two physicians—William Gilbert and William Harvey. Gilbert's *De Magnete*, published in 1600, provided a real starting-point for the development here of experimental physics some 60 years later, through the work of Boyle, Hooke, and other early Fellows of the Royal Society; and with Harvey's *De Motu Cordis*, in 1628, came the real beginning of experimental physiology and medicine for all the world. You remember Harvey's fervid advocacy of the experimental method—veritable battle-cries of his attack on a medicine which, till then, had been based upon the study and interpretation of ancient authorities—"Not from books, but from dissections"; "To search and study out the secrets of Nature by way of experiment"; and, again, "Nature is herself to be addressed. the paths she shows us are to be boldly trodden; for thus only, and while we consult our own senses . . . shall we penetrate at length into the heart of her mystery."

It is noteworthy that Francis Bacon, who was Harvey's patient, paid so little attention to the great practical demonstrations which were given by these two, his English contemporaries, of what could be achieved by the method of direct appeal to Nature, which Bacon, himself no experimenter, was bent on proclaiming as the basis of a new philosophical system. The point of chief interest for our purpose, however, is that Harvey's great example and emphatic injunctions should have had so little apparent effect on his fellow physicians in England during the following 200 years. The unaided observational and descriptive study and naming of diseases as practised by Sydenham, whose career overlapped Harvey's, and by the many who followed him during this long period made very important additions, of course, to that aspect of medical knowledge; but they left problems of aetiology to crude and even fantastic speculation; while it is not surprising that the treatment of diseases should have so long remained so rarely effective and so often detrimental and dangerous. Such, however, was to be the general course of medicine for centuries. Harvey's experimental method passed, meanwhile, almost entirely into the hands of non-medical investigators. When the nature and mechanism of the circulation of the blood had been made clear, the next great step required for the advance of medicine—as Harvey himself had foreseen, though he made no real approach to it before he died—was the discovery of the nature of the respiratory process. This was very nearly achieved before the end of the seventeenth century by the group round Robert Boyle—Hooke, Mayow, and Lower, of whom only Lower had studied medicine—but science was then led astray by the dangerously plausible phlogistic speculation of Stahl, a physician, to be brought back to the true line of advance by the experimental chemist Lavoisier a century later.

Progress in the Nineteenth Century

In this long period, and well into the nineteenth century, Harvey's experimental method seems, indeed, to have commended itself to surgeons more than to his fellow physicians. John Hunter was passionately devoted to the making of experiments; his pupil, the country surgeon Edward Jenner, followed Hunter's suggestions and promptings in the experiments from which came not only a practical protection against smallpox but a seed of knowledge from which were to germinate, much later, the progressive

*An address given on October 10, 1950, in opening a course of lectures on "The Scientific Basis of Medicine" arranged by the British Postgraduate Medical Federation.

experimental sciences that now deal with specific immunity and with the viruses. You remember Hunter's letter to Jenner, with its provocative questions: "But why think? Why not try the experiment?" As late as the 1830's, such advancement of medical knowledge as was due to experiment seems still to have been largely in the hands of the surgeons. Charles Bell, in that decade, recognized afferent and efferent nerve fibres, and the different functions of the spinal nerve roots—an observation which was confirmed and extended, indeed, by the almost simultaneous researches of the French physiologist Magendie, in Paris. Of comparable importance, indeed, was the experimental work on reflex action of a physician, Marshall Hall, published by the Royal Society in its *Philosophical Transactions* in 1833, but received with scepticism and ridicule by leaders of contemporary medical opinion. It was an American Army surgeon again, William Beaumont, who in that period made the first systematic experimental studies of the secretory functions of the stomach and the digestive properties of its juice, using with a brilliant opportunism a gunshot accident which gave him a co-operative patient with a permanent traumatic gastric fistula.

From the middle years of the nineteenth century onwards the advancement of essentially medical knowledge by researches in the experimental laboratories was to provide one of the main currents in the gathering flood of general scientific discovery which characterized that period. First came the great revival of experimental physiology, due to the researches and the inspiring influence of Magendie's great pupil and successor in Paris, Claude Bernard, and, a little later, to the great school of Karl Ludwig, in Leipzig—a movement which, somewhat later again, was to spread to this country, largely at the hands of men who had been the pupils of these Continental pioneers. Then bacteriology, with its later outlet to immunology, was opened up to experimental research as an essentially new domain by the work of Louis Pasteur—who, though not medically qualified, had studied under Claude Bernard—and in Germany by that of Robert Koch, and then by the great host of those who followed the lead thus given; and among the early followers was Joseph Lister, who transformed the whole prospect in surgery by researches based on the analogy between surgical infection and putrefaction, the microbial origin of which had been demonstrated by Pasteur.

Discoveries by British Medical Men

Meanwhile, however, this outburst of activity, this great ferment and expansion of ideas, in the experimental sciences so nearly contiguous in their interests to medicine, would appear to have had much more effect on practical developments in public health administration and of technical aids to diagnosis than on the attitude of clinical authority to experimental research as a method by which medical knowledge could be advanced. British medicine of the middle and later nineteenth century could point, indeed, with justifiable pride to the discoveries then being made by keen observation of disease at the bedside, and by correlation of signs and symptoms with morbid changes in particular organs as seen post mortem. The skill and insight displayed in researches conducted on these slow observational lines by men like Richard Bright, Thomas Addison, or, on the surgical side, James Paget, and the scientific interest and importance of the discoveries thus made, would have justified a claim to distinction in medical research for any period in any country. Nor is it to be doubted that there are important discoveries still to be made by this patient method, which waits for Nature to make the experiments, in directions unpredictable and under conditions of unknown complexity, and contents itself with a faithful record and correlation of results.

One aspect of Harvey's injunction it obeys, in addressing its inquiry direct to Nature. On the other hand, it may be suspected that the very successes achieved by this purely expectant observational method, in this period of the middle and later years of the nineteenth century, may have been among the influences which kept clinical medicine so long aloof, made it seem, indeed, to drift further away from the widening stream of experimental discovery which was fulfilling the other, and major, principle of Harvey's policy. And meanwhile there were changes in the social status of practical medicine which would not, I think, have been conducive to the maintenance of a lifelong devotion, such as Addison had shown, to research by any method. William Gull, Addison's pupil, having won early fame by his work on thyroid defect and myxoedema, achieved it in another direction with the revelation, after his death, of the size of the fortune which an immense and various consulting practice had enabled him to accumulate. Whatever the reason, the cleavage between clinical practice and the experimental researches contributory to medical knowledge tended to become deeper.

In one department of medicine, indeed, that of neurology, this cleavage seems always to have been little if at all effective. Clinical knowledge here was conscious of its need for the analysis of nervous functions, which only the experimental laboratories could provide; while there were responses, especially on the sensory side, of the higher nervous centres which could be studied only by applying an experimental method to the reactions of a co-operative human patient. And so we find a Ferrier or a Horsley working always in the laboratories as well as in the wards, while the clinical researches of Hughlings Jackson were making an essential contribution to the physiology as well as to knowledge of the disorders of the central nervous system. And I have no doubt that cases here and there could be discovered, by search in the more general fields of medicine and surgery in that period, of such conscious co-operation and reciprocal fertilization of ideas between experimental research in the laboratories and practice and observation in the wards. G. R. Murray's discovery, in 1891, of the treatment of myxoedema by administration of thyroid gland comes to mind as an example; its inspiration came even more clearly from Horsley's experiments on monkeys than from Gull's clinical observations; but the very fact that it so readily suggests itself indicates to me that this was a rather conspicuous exception.

Aloofness to Experimental Research

I do not believe that I misunderstand or exaggerate the position in suggesting that, in medicine and surgery as a whole, including most of their special departments, there was in the period under discussion a growing tendency to this aloofness of interests and aims, this progressively dominant assumption that experimental research, and indeed the attempt to apply scientific criteria of evidence with any rigidity, was a matter for the laboratories; and that the practice of the wards, on its part, must be based upon a separate empirical art, ready on occasion to incorporate technical contributions from the research laboratories into the routine of diagnosis or treatment, but basing itself essentially on a body of esoteric experience, trained skill and acquired instinct—an art, a craft, almost a priesthood, not properly a science of any kind, and least of all one seeking to advance knowledge "by way of experiment."

Perhaps there was a connexion between this attitude and the tradition, still current in my student days, that a physician should use no apparatus which could not be carried in his pocket or in his conveniently rigid and capacious tall hat. Even the clinical thermometer was under suspicion, indeed, of causing the loss of a special skill. The earlier physicians, it was claimed, had been able to discriminate among the causes of a fever by the quality of the feeling of heat communicated by the patient's skin to the experienced hand. I believe that that great observer Thomas Addison had been the first to claim that the skin in pneumonia gave a peculiar sensation of a tingling heat. Far be it from me to deride such a claim as incredible; my only concern is to emphasize the absence of any impulse to raise it above the level of such empirical observation. Scientifically, such clinical lore was, indeed, little better than the practice of a prescientific manufacture, depending for its test of the quality or consistency of a product on the experienced eye, nose, or thumb of the old foreman. The clinical attitude threatened to become, indeed, not merely unscientific, but even explicitly antiscientific.

When I say "explicitly" I have in mind the injunction which met me on the threshold of such clinical experience as I was destined to obtain. "When you enter my wards," said Dr. Samuel Gee, "your first duty is to forget all your physiology. Physiology," said he "is an experimental science—and a very good thing, no doubt, in its proper place. Medicine is not a science, but an empirical art, and it is as such that you may learn something of it here." He added that some day medicine, too, might become an experimental science; but that this would not be in his time.

Now Samuel Gee was a fine and scholarly physician—a late representative, and a very good one, of a tradition which then showed no sign of losing its authority. He had made his own distinguished contributions to medical knowledge by the accepted, observational method; his description of the condition which he named the "coeliac disease" was, I believe, as perfect as could be given until the experimental discovery and differentiation of the vitamins provided what was necessary to complete the aetiological picture. Like other honest physicians of his period he was cynically sceptical about most of the medicinal treatment then available; but he prescribed with judgment those few remedies in which his own experience gave him confidence. A case of "Barlow's disease" was admitted to his ward—infantile scurvy, in the first recognition of which, indeed, he had himself been associated with Thomas Barlow—and Gee ordered, not any drug, but raw meat juice and as many oranges as the child could suck. The empirical fact that such a treatment was effective in scurvy had, of course, been discovered, forgotten, and rediscovered in each of several previous centuries, and even made the basis of regulations by the Admiralty and the Board of Trade; but without the authority of the controlled experiments which have more recently established it on a basis of rational scientific meaning it might still be subject to these alternations of recognition and oblivion.

When every physician depended on his own experience, in most cases quite vague and unorganized, each was entitled, of course, to treat a condition of doubtful aetiology according to his own fancy. The situation was similar in the case of rickets. The treatment of this condition with cod-liver oil had been mentioned as early as 1840; in the period of which I am speaking, at the very beginning of this century, it was current gossip that the eminent Bart's surgeon Sir Thomas Smith had recommended it for the rickety lion cubs at the Zoo. Yet in default of controlled experimental evidence the physician could still pick and choose among the suggested causes of rickets, and vary his treatment accordingly. The favoured aetiologies then, so far as I remember them, were an intestinal infection and a defective absorption of fats; the latter being based, possibly, on some vaguely apprehended analogy with Gee's "coeliac disease." Meanwhile, in such a confusion of competing speculations and unorganized experience, rickets continued to flourish in our industrial communities, with nothing effective done to treat it, and nothing at all to prevent it. Well might the community have cried aloud, with John Hunter, "But why think? Why not try the experiment?" The experiments, however, which would at last give definite evidence concerning the origin of rickets, and provide a basis for the action which would practically eliminate it, were not to be made till some 15 years later by Sir Edward Mellanby, who is to give the first of the special lectures of this series.

To what, then, are we to attribute this aloofness, even antagonism, of the predominant clinical attitude of those days to the same application of the experimental method to problems in the field of medicine as had been so successful in other departments of natural science? Instinctive defence of authority from subversive intrusion would no doubt account in part for the reaction. A priesthood does not readily share its privilege, or accept additions to or corrections of its doctrine from outside the pale; while the advocates of the scientific method, on their part, would inevitably, with Harvey, react against authority as inimical to its spirit. But I think that we may find a further clue to this antagonism in a warning which, as late even as 1932, was given to his students in a lecture, and repeated with emphasis, by one who was assuredly no opponent of the proper use of the scientific method in medical research—the late Wilfred Trotter. "A practical art," he warned them, "which pretends to be an applied science does not show itself to be progressive, it only shows itself to be quackery." And I think it can hardly be doubted that such shallow pretence to find direct application, in the clinic, for experimental results, even when their soundness and their meaning were still largely matters of conjecture, was too obvious in the practice of some physicians early in this century; and contempt for such posturings must surely have sharpened the reaction of the sound physician of the old school, conscious that, within its own limitations, his cautious if unduly complacent empiricism had really more of the true spirit of science, in spite of his emphatic disclaimer.

A Change in Outlook

Our proper concern to-day, however, is not with the causes contributory to the position half a century ago, but rather to inquire into the causes of the remarkable change, the veritable transformation, which began not many years later, leading to to-day's increasingly co-operative relation between genuine research in the wards and researches in a large and still growing number of the natural and experimental sciences. How has it now become possible and natural to plan for such a series of lectures as will follow this one, dealing with so many aspects of "the Scientific Basis of Medicine," and to refer, without apology or hesitation, to "Scientific Method in Medical Research"? We cannot expect to recognize or to evaluate all the various factors which have contributed to this change. I must be satisfied to draw attention to a few.

We ought first to note the rapid spread—thinking of Harvey, we ought to call it a revival, perhaps—of the belief that a direct study of disease in the human patient can

partake of the nature of a genuinely scientific research. It may be purely observational, it may be experimental in its method; but, in either case, it is ready now to accept the controls and submit to the discipline of the scientific method, and no longer seeks escape from these on a plea that medicine is, and, by implication, can be content to remain, an empirical art and not a science. What has brought about the change? It has had enthusiastic advocates, like the late Sir Thomas Lewis, who insistently claimed for clinical research the status not merely of a science but of a separate *experimental* discipline, as independent, in its aims and its methods, of the physiology and pathology of the laboratories as these of other experimental sciences. I am sure that Lewis, with his burning conviction, did invaluable service to the encouragement in this country, lagging behind some others in that respect, of interest in clinical research as a career, and of enterprise in the provision of opportunities for it. It seems to me, on the other hand, that, with his own research activities concentrated on the physiological analysis of symptoms, he tended to exaggerate the possibilities of experiment on the human subject. There are obvious and natural limitations to experiments directly on man, in researches on aetiology, for example, and even, until a final and confirmatory stage, on therapeutics. Overemphasis of the scope of the experimental method in the clinic may tend, I think, to obscure the most important feature of the new and more general development, which so many of the lectures of this series will illustrate—namely, the progressive obliteration of the earlier deep division, the reciprocal aloofness, between the researches directed to the advancement of medical knowledge in the clinics and those making equally essential contributions to it from the experimental laboratories.

We must recognize, further, that the approach to this easier understanding has been made from both sides. Not only has there been a rapidly increasing readiness on the part of the clinics to adopt, or to interpret, as Wilfred Trotter would have it, the new knowledge pouring from the experimental laboratories; an increasing number of researches in a widening range of the experimental sciences have been undertaken with a conscious orientation towards the advancement of biological and ultimately of medical knowledge. But the most important result, I believe, of this more intimate understanding has been a growing recognition of the need and the duty to interpret the evidence produced, whether it comes from clinics or laboratories, whether from opportunist observations or from deliberately framed experiments, by common and rigid standards of scientific validity and significance.

I spoke of researches in the experimental sciences which have had in view the possibility of service to medical knowledge; it seems hazardous, however, if not impossible, to predict of any scientific discovery to-day, however remote its immediate or conscious objective, that it can never find medical application. Who would have foreseen that the effect of a magnetic field on the path of an electron, or the fission of heavy atomic nuclei under neutron bombardment, would have any special bearing on medical researches? Yet the electron microscope and the newly available radioactive isotopes seem, so far, to have found their readiest and perhaps their most important applications in researches contributory to medicine. Plenty of other examples could be found, and many, indeed, will be furnished by special lectures of this series. I must be content, however, to mention a few of the more general developments in experimental science which seem to me to have exercised an especially potent influence on the course of medical research and on the growth of the newly co-operative relations between the clinics and the laboratories.

The Influence of Biochemistry

I think that I should place first, for influence in that direction, the rapid penetration, by chemical ideas and chemical methods, of experimental physiology, pathology, therapeutics, and, indeed, a much wider range of the biological sciences. Biochemistry, as we know it to-day, is essentially a creation of the present century. When I was a student at Cambridge, chemical physiology, as we called it, was in relatively low esteem even with the physiologists, and in lower still with the chemists—a Cinderella in the scientific household. "Tierchemie ist Schmierchemie"—animal chemistry is a chemistry of messes—was an aphorism widely quoted and attributed to the great Emil Fischer, then the recognized European leader in organic chemistry. Yet Fischer, by applying the methods of exact chemistry to attack the complex structures of the sugars, and then of the proteins, was himself becoming one of the pioneers of a development which in a few decades was to give to the new biochemistry a place of central importance among the medical and biological sciences.

And then, just before the new century began, the late Frederick Gowland Hopkins came to Cambridge, where, by the influence of his own researches and teaching, and by his steady championship of its potential significance and scope, he was to play a leading part in the movement which has enabled biochemistry so rapidly to permeate and to give a new orientation to ideas and methods in medical research, in the clinic as well as in the experimental laboratories. And, in years more recent, the results which biochemistry was thus achieving by use of the more fundamental chemical disciplines have brought a major and progressive part of organic chemistry, with great new resources of knowledge and of methods acquired in other studies, back to its original aim—the investigation of substances of biological origin and interest—and thus into contacts, now ever more numerous and intimate, with medical research and with clinical medicine.

Look at the list of the lectures of this series, and observe how large a proportion of them deal with medical advances involving applications of exact methods and fundamental principles of chemistry—lectures dealing not only with problems of animal and human nutrition, metabolism, excretory and respiratory functions, with hormones and vitamins, but with conditions of bacterial growth, tissue defences, immunity reactions, and with the chemotherapy of infections. I make only a quick selection as I glance at the list.

Immunology and Chemotherapy

In connexion with advances in immunology and chemotherapy, which have produced in recent decades so conspicuous a revolution in the methods of preventing and treating infections, we may note again how dominant was the influence of chemical knowledge and chemical conceptions on the pioneer investigations, and, indeed, on the whole of the experimental strategy, of the late Paul Ehrlich and of those who have followed his inspiring lead. And could we find anywhere a more complete illustration of the influence of chemical ideas and discoveries on the progress of medical knowledge, or of effective co-operation between researches in the clinics and in the laboratories, than that offered by the recent work of Hench and Kendall, of the Mayo Clinic, on the remedial effects of cortisone and A.C.T.H. on rheumatoid arthritis, on rheumatic conditions in general, and on a still widening range, apparently, of abnormal protective or allergic reactions? Dr. Hench is

in fact, lecturing on that subject at this moment at the Royal Society of Medicine. Clearly no approach to a discovery so brilliant in its immediate achievement and in its promise of further developments could have been made without the years of systematic laboratory researches by Kendall and others on the difficult and complex chemistry of the hormones of the adrenal cortex, or without other experimental knowledge of the effects of chemically differentiated specific hormones of the pituitary anterior lobe on the activities of different ductless glands. But, on the other hand, to bring all this wealth of discovery from the laboratories to this particular focus and practical trial evidence was required, which only expert clinical researches could have supplied, concerning the remissions of rheumatic or allergic conditions occurring regularly in circumstances which had been shown to raise the output of the adrenal cortical hormones—an observation made possible, once again, by the application of chemical knowledge and chemical methods to material made available by the use of clinical opportunities. Those of you who attend the full series of these lectures will have the opportunity of observing many other examples of the part thus played by chemical methods and ideas in medical research as we now know it.

Biophysics

Good cases could be made, no doubt, for the significance, in the development which we are considering, of advances in other departments of fundamental science. Physics, for example, was very early represented by the rapid exploitation of the *x* rays in diagnosis; more recently it has offered many applications of the modern resources for amplifying and recording small variations of electrical potential, as in electrocardiography and electroencephalography. I think, however, that it can fairly be suggested that such advances in physical knowledge and technique have hitherto been largely used in medicine as devices for record and diagnosis, and that physical ideas in themselves have so far not so powerfully affected the general direction and outlook of medical research as have those derived from biochemistry. The fundamental physiology of muscular and nervous activity has, of course, been immensely enriched by use of the methods which modern physics provides. These have enabled us to recognize, to record, and to measure fleeting and otherwise imperceptible changes and to make proximate analyses of natural complexities of these into unitary components; but always with the presumption that the electrical changes thus detected and analysed are but signals of ultimately biochemical phenomena. The coming generation may, nevertheless, find biophysics rivalling or even replacing biochemistry in its influence on the course of medical research and the directions of medical thought.

The Science of Statistics

If, however, I were asked to choose one other among the more fundamental scientific activities as a competitor with biochemistry in these recent decades, for depth and range of influence on thought and practice in medical research, I should name the science of statistics. Quietly but irresistibly, it seems to me, statistical methods and principles have been exercising and establishing their corrective influence, substituting a numerical measure of the evidential significance of data obtained in ward or laboratory, whether from opportunist observations or deliberately planned experiments, for the vague and speculative methods of appraisement which formerly prevailed.

Two lectures of this series, by Professor Bradford Hill, will furnish detailed illustration of this salutary influence of statistics on medical research. This bracing discipline was as badly needed in the laboratories as in the wards; and from both sides came signs of shivering discomfort, as an early reaction to the cold jet of statistical reason. It must indeed have been painful to a mind proudly reliant on the experience of half a lifetime to submit to the imposition of control experiments and statistical evaluation of results as a protection against an unconscious bias of its judgment. To name an example of topical interest, it may be regarded as practically certain that uncontrolled clinical testimony would, but a few decades ago, have given an extended currency, at least, to confidence in the proved value of the antihistaminic substances as suppressive remedies for the common cold.

On the other hand, the value of a statistical criticism of methods and results has been at least as obvious in the experimental laboratories of medical science. It was especially needed, I think, in connexion with the common type of experiment in which an attempt is made to determine the smallest quantity of a remedy, or other preparation, producing death or some other limiting reaction—what my former colleague, Professor Gaddum, conveniently termed a "quantal response." The problem was first presented in its true perspective, I believe, in a paper in which results obtained by the late Sidney Rowland with a plague-bacillus toxin were analysed by the late Professor Major Greenwood, to whose influence and teaching during many years medical science has been immensely indebted for the clarification of its ideas in this direction. Professor R. A. Fisher's investigations and writings have also achieved the authority of classics in a wider range of biology; while as contributors, in this country, to the building of a scientific statistical basis for the procedures involved in the "biological standardization of remedies," the names of Trevan, Gaddum, Emmens, and, most recently, Perry are worthy of special recognition.

Earlier to-day I was waiting at a multiple bus-halt at which buses of every line due to stop there seemed to arrive in rapidly repeated succession, except that which I wanted. And it occurred to me that a conclusion, that my line had somehow been eliminated, could have been based on reasoning not very different from that which passed muster not only in the wards, but often in the experimental laboratories, in my early days as student and research worker. And when I had despairingly departed in a taxi my successor at the halt would probably have concluded that buses of the line for which I had waited in vain predominated among those stopping there; and so we should have had the familiar and discouraging conflict of scientific evidence.

Even now I suspect that there may still be found, here and there, authors of medical publications, both clinical and experimental, whose tentative sips at the Pierian spring of statistical method have produced in them little more than a conviction that the occurrence of a particular event—death, say, or recovery—in two out of three instances will become scientifically precise and significant if they record it as a percentage—66.6%. In general, however, I am sure that the calm and ruthless logic of the statistical method has had an influence of inestimable value, in giving a higher level of scientific authority to the planning of investigations and the appraisement of their results, over the whole field of medical research; and that, in thus imposing common standards of scientific validity and quantitative significance on researches in the field, in the wards, and in the laboratories, it has been a most potent factor in the newly co-operative relationship.

Opportunities for Research Work

Let me now make brief reference to the important part in promoting this growth and integration of scientific activities in medical research played by the great changes which have occurred in the source and the scale of the material provision available for its support. Those of us who wished to try our hands at research in the medical field at the opening of the century competed hopefully for the rare crumbs of brief opportunity, which then fell infrequently from a few small private endowments. You know how profoundly that position has been altered. With much larger funds available from private generosity, and with even more important and steadily expanding grants of public money, administered by the Medical Research Council or dispensed through the University Grants Committee, no man with a genuine impulse and with an adequate equipment of training and temperament for medical research need fail now to find an opportunity to prove his aptitude, and, if the result be favourable, to give medical research then at least a prominent place in his life's plans and ambitions. I am one of a great number who have reason to be grateful for the opportunities which have been created under this new dispensation.

There have been and may still be some, however, who, while they would acknowledge that the results, so far, appear to have been broadly beneficial, are doubtful and suspicious concerning the ultimate effects of this predominant support from public funds on the freedom of medical research, and therewith on its long-range effectiveness, as well as on its scientific spirit. Up to a point I can understand this anxiety, considering what might happen under an administration less wise and sympathetic, less expert and independent, than that which has hitherto been responsible for the effective decisions.

The anxiety in question is not unconnected, I think, with a more general discussion, now current, of the proper aim of research in all departments of science. You will no doubt have heard it argued by some that the proper aim of research is to discover truth for its own sake, and by others that it is to discover means for the material improvement of the lot of mankind. If you follow the arguments in detail, however, you will find that those who advocate the pursuit of knowledge for its own beauty and excellence often support their claim by evidence that this has led to the widest and most beneficent of practical developments; while those who insist that material benefit is the proper aim justify encouragement of the most abstract researches as an eventual contribution to that practical end. One begins to wonder, indeed, whether there is much to choose between these rival creeds. It has to be remembered however, that the advocacy of material human benefit, as the only acceptable aim, has associations with a particular political philosophy, and thus with plans for a central, authoritative direction of research. Theories, like people who seem innocent in themselves, may prove to be dangerous through the company they keep.

The Ultimate Aim

In dealing with medical research, in particular, material benefit to human life and health must surely be accepted as the ultimate aim; I can find no other meaning for the word "medical" in such a connexion. And our chief concern must be to ensure that the public funds directly granted for medical research continue to be administered and allotted, as hitherto, by a Council composed predominantly of experts who know the meaning of research, and who can be trusted to recognize the ways in which its truly scientific pursuit can most effectively be encouraged, without either facile enthusiasm or obstinate caution. Such administrators will know from their own experience that, while the consciousness of the ultimately philanthropic purpose must be retained, and may even provide a valuable stimulus, success in medical research very often depends on an investigator's freedom to seize and to follow an unexpected clue, even when it appears to lead far from the original objective, and in a direction offering no visible likelihood of practical developments. They will be aware of the danger of short cuts, taken in the hope of reaching some dramatically practical result, without submission to the full and exacting discipline of science; and they will know how to hold and adjust the balance between the claims of researches undertaken to develop existing knowledge for medical uses and of those which plan bolder adventures into the unknown. While the administration remains safely under such expert and independent control, the support of medical research from the public funds, now an indispensable condition of its pursuit in this country on the present progressive scale, will continue to be protected from any serious danger to its freedom and integrity. Such danger could arise only if the distribution of the available funds were to become subject to political pressure, seeking to influence its direction in order to satisfy some popular clamour or sentiment, to meet some official convenience, or to enhance some Minister's prestige.

LABORATORY AND CLINICAL EXPERIENCE WITH TERRAMYCIN HYDROCHLORIDE

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A comparatively recent addition to the field of chemotherapy is the new antibiotic "terramycin hydrochloride," first reported in America by Finlay *et al.* (1950). This substance was obtained as a pure amphoteric compound from the growth of a soil actinomycete, *Streptomyces rimosus.*

There is already an extensive American literature, and much is in course of publication, on the physical, chemical, bacteriological, and clinical properties of terramycin (Finlay *et al.*, 1950; Hobby *et al.*, 1950; Welch *et al.*, 1950; Herrell *et al.*, 1950; Bliss *et al.*, 1950).

Terramycin hydrochloride is a sulphur-coloured compound with a bitter taste. It is sparingly soluble in water at *p*H 7, but can be readily dissolved by the addition of NaOH to *p*H 8.3–8.5, forming the sodium salt, or by adding HCl to lower the *p*H to 2, when the hydrochloride becomes soluble

Stability

In contrast to "aureomycin," terramycin is a relatively stable antibiotic in solution. We have found that the acid solution at *p*H 2 maintains its potency for up to 30 days when kept at 0° C. as judged by assay against a standard staphylococcus. The alkaline solution maintains its potency for about seven days at 0° C., but it slowly deteriorates thereafter, turning dark brown in colour, and forms a

precipitate due to hydrolysis. This precipitate when redissolved still possesses considerable activity.

The stability of the hydrochloride in human serum was found to parallel closely that of the aqueous solution. The terramycin level in sera kept at 0° C. showed no appreciable fall in seven days. The effect of heat is shown in Fig. 1. A temperature of 100° C. is necessary to

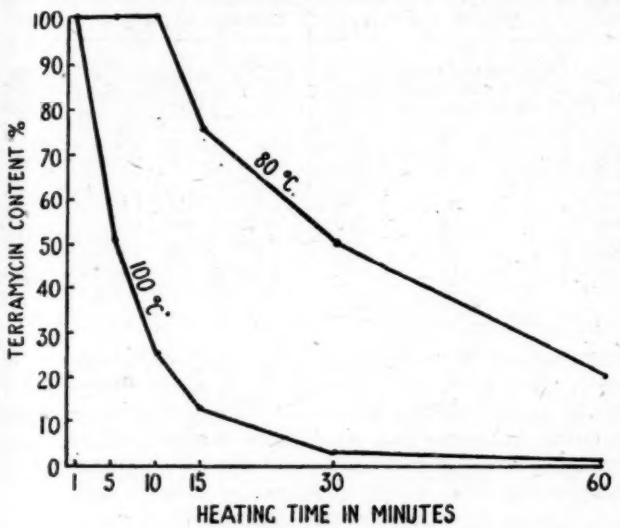

FIG. 1.—Effect of heat on solutions of terramycin of strength 160 μg./ml. at *p*H 7.

inactivate completely a terramycin solution of 160 μg./ml. in 60 minutes at *p*H 7, there being little deterioration in 10 minutes at 80° C. The latter temperature and time suffice to sterilize contaminated fluids such as urine prior to assaying its antibiotic content. A lower concentration of 16 μg./ml. was completely inactivated in 30 minutes at 100° C. The relatively stable character of terramycin hydrochloride solution makes it a much more satisfactory antibiotic than aureomycin from the point of view of the laboratory worker.

Laboratory Assay

The standard techniques for the assay of other antibiotics have been tried with equal success for terramycin hydrochloride. In practice an inoculum of 10 c.mm. of an overnight broth culture of the Oxford staphylococcus to 10 ml. of digest broth was used to assay the antibiotic in aqueous solution, serum, urine, or filtrates of faeces. The microcapillary technique of Fleming and Smith (1947), while very convenient, was found to give growth at slightly lower dilutions than with the tube dilution method which was used as a routine. The familiar "filter-paper disk," "cork-borer hole," and "ditch" techniques applied to other antibiotics can also be used for rough sensitivity tests with terramycin. In practice the organisms isolated from patients treated with the antibiotic were all assayed by the serial dilution method in broth and read at 24 hours to give as accurate a picture as possible of their sensitivity and to observe any development of resistance. The standard solutions of terramycin hydrochloride used in these series of investigations were all prepared at strengths of the order of 2,500 μg./ml. and dissolved in dilute HCl at *p*H 2 and kept frozen solid. Dilutions for assay were made from these stronger stock solutions and were replaced approximately every three weeks. This has been found to be more satisfactory than using the less stable though highly soluble alkaline solution at *p*H 8.5.

Blood serum levels were assayed using the Oxford staphylococcus in tubes in broth as mentioned above; urine was first diluted 1 in 10 and then used similarly Faeces concentrations were estimated after emulsifying 1 g. in 10 ml. of distilled water, centrifuging, and heating the supernatant at 80° C. for 10 minutes for sterilization

Bacterial "Spectrum"

As with chloramphenicol and aureomycin, terramycin hydrochloride is a "broad-spectrum" antibiotic. Table I shows the range of sensitivity of some of the commoner

TABLE I.—*Sensitivity of Some Commoner Micro-organisms to Terramycin Hydrochloride*

	Lowest Inhibiting Concentration (μg./ml.)
Staph. aureus	0·25
Haemolytic streptococcus Group A	0·125–0·25
" " " B	0·5
Str. pneumoniae	0·25
" *faecalis*	0·5
" *viridans*	0·25
C. diphtheriae (mitis)	0·25
Cl. welchii	0·5
N. gonorrhoeae	0·25
Bact. coli	1·0–20·0
" *	1·25
" *friedländeri* (Kl. 41)	3·0
H. influenzae	5·0
Salm. typhi	1·0
" *typhi-murium*	1·0
Sh. flexneri	1·0
Pr. vulgaris	200+
Ps. pyocyanea	5·0–200
B. anthracis	0·25
" *subtilis*	0·25
" *cereus*	0·25
M. tuberculosis H37Rv†	12·5
" *phlei*	4·0

* Mutant resistant to 500+ μg. of streptomycin per ml.
† Ten days' incubation, Dubos medium at 37° C.

micro-organisms so far tested. It will be seen that the antibacterial activity follows aureomycin closely. In general it is highly active against Gram-positive cocci and Gram-negative cocci. The intestinal group of Gram-negative bacilli are usually sensitive to concentrations below 10 μg./ml., with the exception of *Proteus vulgaris* and some strains of *Pseudomonas pyocyanea*. However, most strains of *Ps. pyocyanea* have been found to be relatively sensitive to concentrations as low as 5–15 μg./ml. (Of a total of 35 strains tested, 24 were sensitive to concentrations below 15 μg./ml.)

American investigators (Hobby *et al.*, 1950; Snyder *et al.*, 1950) report marked activity against the brucella and rickettsia. It is also reported to have a highly potent *in vitro* effect against *Entamoeba histolytica* (Most *et al.*, 1950), but little or no activity against viruses (Quilligan *et al.*, 1950).

Development of Bacterial Resistance.—During the treatment of the cases described, no resistant mutants of originally sensitive strains have appeared; particular attention in this respect has been paid to strains of coliform bacilli in urinary infections. *In vitro* experiments indicate that with some coliform strains a slow step-like resistance can be evoked, but there has so far been no occurrence of any "streptomycin-like" resistance.

Toxicity.—American reports (Pan *et al.*, 1950) show that the LD50 doses of terramycin hydrochloride for mice are 140 mg. per kg. intravenously and 2,240 mg. per kg. orally. This suggests that its behaviour in this respect is very similar to that of aureomycin, the corresponding figures of which are 134 mg. per kg. intravenously and 2,500+ mg. per kg. orally (Harned *et al.*, 1950).

Experimental Administration

Intravenous administration of terramycin in saline was undertaken, a rabbit of 2,400 g. weight being used. Fig. 2 shows the results of periodic serum and urine assay following a dose of 40 mg. per kg. body weight. This was the largest dose used during these investigations, and it gave rise to

slight incoordination and twitching, coming on two minutes after injection; these signs lasted about one minute. These symptoms may well have been due to the use of an

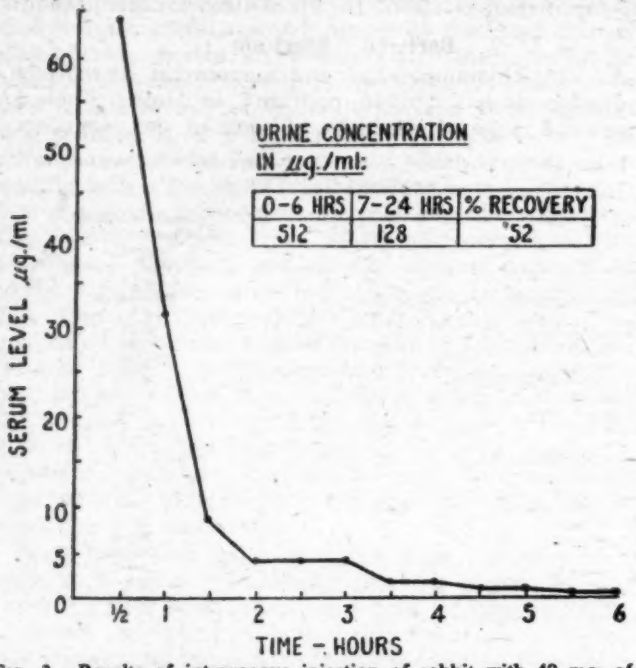

FIG. 2.—Results of intravenous injection of rabbit with 40 mg. of terramycin hydrochloride per kg. body weight (total 100 mg.).

unbuffered solution. There were no side-effects observed when smaller doses of the order of 20 mg. per kg. body weight were given intravenously to the same animal.

Administration of Single Doses to Man

The response of human volunteers to oral administration varied. Fig. 3 shows the average serum level obtained after a single dose of 250 mg. to healthy young males and the average response to a single dose of 1,000 mg.

It had been noted previously (Herrell *et al.*, 1950) that the levels of terramycin obtained in blood and urine bore little apparent relation to the dose ingested, though on the whole the higher doses resulted in the production of higher levels. These observations were usually concerned with single-dose administration, though some of them recorded multiple-dose levels.

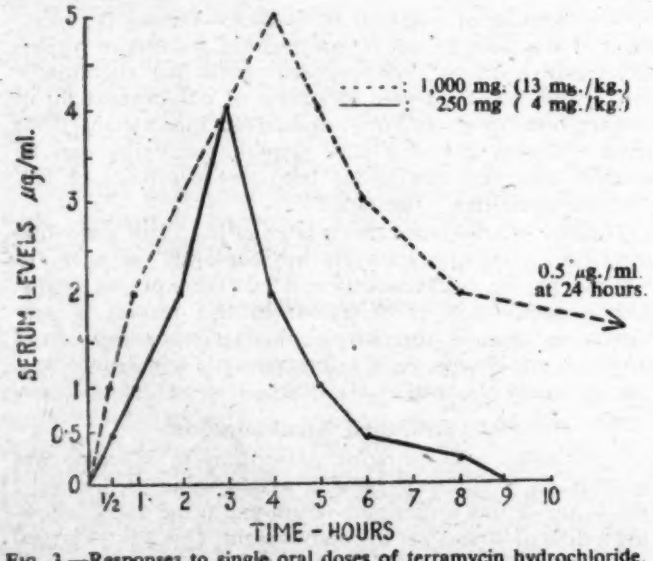

FIG. 3.—Responses to single oral doses of terramycin hydrochloride. Each point is average of four investigations.

Early experiments showed that urine and serum levels tended to rise for the first 24 hours on six-hourly dosage, but thereafter rose no further. We accordingly determined serum and urine levels, after the first 24 hours, on 27 patients who were having courses of terramycin lasting from 5 to 10 days (Table II).

TABLE II.—*Showing Oral Dosage and Concentrations Attained in Serum and Urine of 27 Patients (µg./ml.)*

Dose mg./kg.	No. of Cases	No. of Serum and Urine Observations	Average Serum Level	Range Average Serum Level	Average Urine Level	Range Average Urine Level	Ratio Urine/Serum
0–10..	1	2	0	—	25	—	—
10–20..	1	4	0	—	100	—	—
20–30..	Nil						
30–40..	2	8	1·25	0–2·5	100	50–150	
40–50..	4	30	5·7	3·5–8·7	165	100–325	29
50–60..	1	2	10·0	—	260	—	26
60–70..	4	18	7·7	4·5–10·0	205	120–250	27
70–80..	6	20	6·8	5·0–9·0	230	120–500	34
80–90..	4	16	8·1	3·5–10·0	240	100–400	29
90–100	4	16	6·9	5·0–11·25	490	250–750	71

Several sets of observations were made with samples of serum taken at various times during a single-dose period—that is, usually six hours—and these, though showing some variation, maintained a moderately stable level. It was concluded from these findings and our earlier experimental observations that, except perhaps for ease of administration, dosage need not be more frequent than six-hourly.

Doses were calculated on a basis of mg. terramycin per kg. body weight. Analysis of the original data showed that on a particular dose schedule some persons maintained higher blood and urine concentrations than others; it was noted that a high blood concentration usually ran *pari passu* with a high urine concentration. It has not yet been possible to relate these differences to increase or decrease of faecal excretion, as our data on this point are incomplete.

To compensate for the different number of estimations on serum and urine in individual patients, the figures for each patient were averaged before incorporation in Table II. This table shows the average and the range of the serum and urine levels obtained at various dose levels. Figs. 4 and 5 show the average of the serum and urine concentration for each case plotted against dose, with the average put in at each 10 mg. per kg. step. The wide variations in the levels are well seen from these graphs, but they also illustrate that, with a sufficient number of cases, levels tend to rise progressively with the dose.

The sharp rise in urine values and the urine/serum ratio at the highest-dose level is of considerable interest, and seems to indicate that, if absorption from the gut increases with greater doses, higher blood levels will not be reached owing to spill-over into the urine. This suggestion gains weight from the fact that, though we have on occasion administered high doses experimentally, we have never recorded a serum level greater than 12.5 µg./ml., though this level has been reached several times.

These dose curves suggest that even for severe infections a total dosage of 70 mg. per kg. daily at six-hourly intervals will give maximal blood levels, while numerous patients will attain such levels on about 50 mg. per kg. daily; lower dosage than these would need control by blood-level determinations.

The study of the urine levels related to dosage shows that terramycin is excreted in high concentrations and that adequate levels can be attained on very small dosage. As will be seen from the earlier data and, later, from the clinical section, most of the common urinary pathogens are susceptible to less than 10 µg./ml.; no dose that we have

yet administered has given levels as low as this. Certainly it would seem from these data that 50 mg. per kg. daily would be more than an adequate dose for most urinary infections, and half this dosage would probably be satisfactory. It is, however, one thing to consider this question

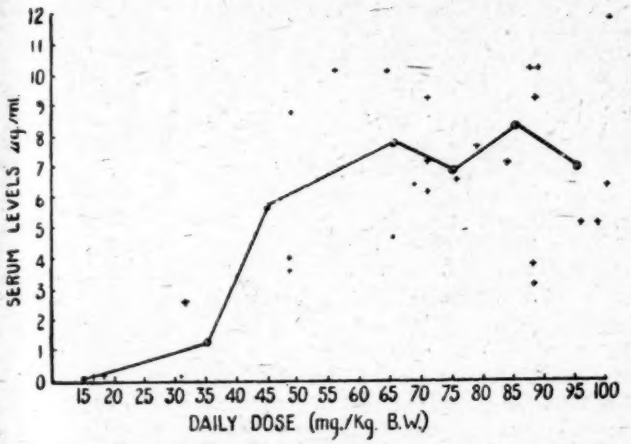

FIG. 4.—Relation between serum level and dose (oral). + Average serum levels for each case. ⊙——⊙ Average serum level as calculated from Table II.

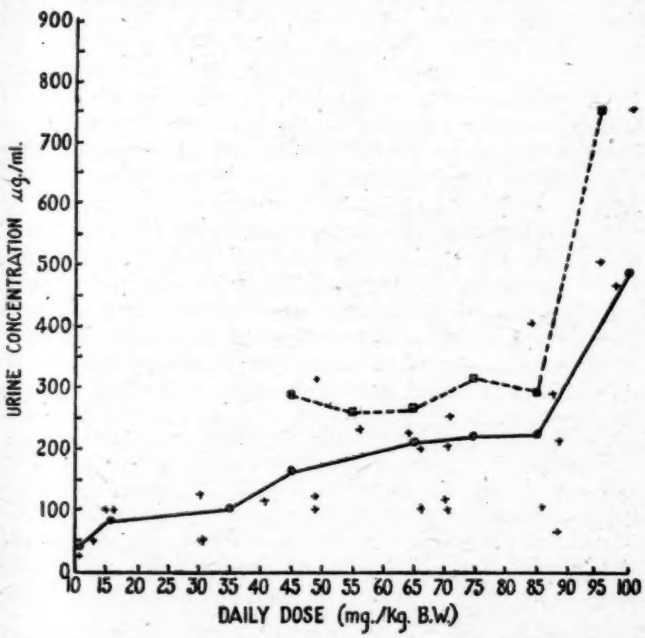

FIG. 5.—Relation between urine level and dose (mg./kg. body weight). + Average urine levels for each case. ⊙——⊙ Average urine levels as calculated from Table II. ⊡----⊡ Ratio urine/serum × 10 as calculated from Table II.

from an *in vitro* angle and quite another to deal with an infection *in vivo*, and we should like to emphasize at this stage that our clinical experience has been mostly with 50 mg. per kg. or greater.

Passage through Serous Membranes

Our experience of terramycin levels other than in the serum, urine, and faeces has been small, but in view of the comparatively recent discovery of the drug the following incomplete data may be of interest.

In one case of Reiter's syndrome with effusion into a joint, after 48 hours' treatment analysis of the joint fluid showed 2.5 μg. of terramycin per ml., the serum level being 5 μg./ml. In one case of pleural effusion after 24 hours' terramycin administration the pleural fluid level was 2.5 μg./ml., whilst the serum level was 5 μg./ml. One case with a biliary fistula showed a very high level (50 μg./ml.) in the bile with quite moderate serum levels.

American experience indicates that terramycin passes into the cerebrospinal fluid in low concentration only, at least in normal persons. It seemed to us that a more useful approach might be to test the passage of terramycin into abnormal meninges, since the intrathecal passage of the drug would be only of therapeutic interest in such persons.

We accordingly selected six cases suffering from tuberculous meningitis; these cases would have abnormal meninges, and we were in addition interested to see whether bacteriostatic concentrations to the tubercle bacillus (probably 10–20 μg./ml.) could be produced in the theca.

Owing to the fact that these cases were having streptomycin and it was not possible to stop this during the experiment, we had to use a highly streptomycin-resistant but terramycin-sensitive *Bact. coli* as the test organism. Under such conditions it was not possible to detect the presence of less than 1 μg. of terramycin per ml.

In all of these cases the meningitis had largely settled down. In no case after 24 hours, despite serum levels between 5 and 10 μg./ml., was there a detectable C.S.F. level; and after 72 hours, during which these high serum levels were maintained, only three out of five cases had approximately 1 μg./ml. present in the C.S.F.

Probably in bacterial meningitis these figures would be improved, but we have as yet no data to support this assumption.

Effect on Intestinal Flora and Concentration in Faeces

The effect on the normal intestinal flora was investigated in eight cases receiving 1 g. of terramycin six-hourly. Specimens of faeces were examined the day before administration began, and daily specimens were examined during the four days in which the drug was ingested and after administration ceased.

After 24 hours' administration the colonies of coliform bacilli and faecal streptococci were diminished, and were eliminated entirely in all cases by the third day. The normal flora became replaced by a heavy growth of *Pr. vulgaris* in four cases, *Pr. morgani* in two, and in two a heavy growth of a yeast appeared; one of these also produced a few colonies of an atypical coliform which was found to be resistant to 200+ μg. of terramycin per ml. Transient appearance of a few colonies of relatively resistant strains of *Ps. pyocyanea* was noted in two cases; these disappeared as administration proceeded. Our observations show that with three days' oral administration of terramycin complete alteration of the flora results. One case of ulcerative colitis produced a sterile specimen of faeces after three days' treatment.

Fourteen observations on the concentration of terramycin in the faeces were made on six cases receiving doses between 66 and 87 mg. per kg. daily. The results after the first 24 hours ranged from 500 μg./g. faeces to as high as 4,000 μg./g. Most of the estimations were grouped round 1,250 μg./g. Such high concentrations as these fully explain the remarkable effects produced on the bacterial flora of the gut, since all gut organisms with the exception of various strains of Proteus are susceptible to concentrations many times less than those obtained (see Table I).

Faecal excretion does not tend to rise after the first 24–48 hours. Terramycin is usually present in the faeces in moderate concentration for one to two days after cessation of treatment. There was no appreciable absorption

from the rectum, since two trials of 2 g. administered rectally as a buffered solution at *p*H 8 in the form of sodium salt gave no detectable blood levels.

We cannot yet say whether this high faecal concentration is wholly the result of a proportion of the ingested dose being unabsorbed or whether some part of the terramycin is excreted into the gut by means of the bile or in other ways.

Clinical Experience

So far our clinical experience has been limited to the treatment of 29 cases; the results in four could not be assessed.

Urinary Infections

Thirteen cases of urinary infection have been treated; seven of these were uncomplicated by demonstrable anatomical abnormality of the urinary system, while the other six had complications such as hydronephrosis, vesical diverticulum, prostatic obstruction, or urethral stricture. Ten cases had been treated previously with sulphonamides or antibiotics, and the organisms all showed resistance to one or more chemotherapeutic agents. All cases were given doses at six-hourly intervals to a total amount of 50–80 mg. per kg. daily.

The pathogenic bacteria involved in the seven uncomplicated cases were either *Bact. coli* or *Str. faecalis*, or both. Sensitivity of these organisms ranged from 1 to 10 μg. of terramycin per ml.

All cases showed a rapid response, catheter samples being sterile at the end of either 24 or 48 hours; treatment was continued for at least 48 hours after the first sterile specimen, and no relapses have so far been seen. Constitutional symptoms were also rapidly controlled.

The results in all the cases with complicating mechanical factors show several features of interest. One case with unilateral hydronephrosis, urethral stricture, and diabetes showed a heavy urinary infection with *Bact. coli* and *Str. faecalis*. Numerous agents had been administered for the control of this infection without success; after one week's treatment these organisms disappeared, becoming replaced, however, by *Pr. vulgaris*. This occurrence did not interfere with the complete symptomatic relief afforded.

Two cases of post-prostatectomy infection and one of prostatic obstruction, all infected with *Ps. pyocyanea* and other organisms, were treated. The sensitivities of the strains of *Ps. pyocyanea* ranged from 3 to 10 μg. of terramycin per ml. All three cases showed very heavy infection; one case was cured after a week, one case responded rapidly but relapsed after treatment ceased, with the appearance of *Pr. vulgaris* and recurrence of *Ps. pyocyanea*. The third case responded rapidly until a resistant atypical coliform organism appeared for the first time, requiring chloramphenicol for its control. Unfortunately these cases were treated at a time when there was a temporary shortage of the drug; longer treatment with higher dosage would probably have been even more effective. Further work is in progress on the important question of *Ps. pyocyanea* infection, as, despite earlier American reports that most strains are resistant, nearly three-quarters of the strains isolated in these laboratories are sensitive to therapeutic concentrations of terramycin. Observations made upon urinary *p*H during treatment did not suggest that the control of this factor was of any great importance in producing cure.

Superficial Infections

A case of erythema multiforme bullosa with pyodermia showed a rapid response to treatment. This was a severe case in a frail old lady infected with *Staph. aureus*, *Bact. coli*, and *Str. faecalis*. These organisms were inhibited by 0.5–5 μg. of terramycin per ml. but showed high resistance to all other antibiotics except aureomycin. A heavy nasal infection with *Staph. aureus* was also present. A course of 14 days' treatment was given; at the end of six days nasal swabs were sterile and skin swabs gave a very scanty growth of *Staph. aureus*. An immediate clinical effect was seen; the lesions dried and the heavy purulent discharge ceased, while skin-healing began and proceeded rapidly.

Another case of severe superficial sepsis was seen in the case of a girl of 12 who had had burns involving about one-third of the body surface two months previously. The child had experienced a very stormy illness, and long courses of penicillin, streptomycin, and chloramphenicol had failed to control the infection. Swabs showed *Staph. aureus* sensitive to 6 μg. of terramycin per ml. and *Ps. pyocyanea* sensitive to 15 μg./ml. After seven days' treatment *Ps. pyocyanea* had disappeared and only scanty colonies of *Staph. aureus* were seen. The appearance of the infected areas had undergone a complete change; the raw areas seemed healthy, the skin edges were advancing fast, discharge was minimal, and the patient's general condition had greatly improved. Skin-grafting was later possible.

A further case of *Ps. pyocyanea* infection was seen in a woman aged 23 suffering from spina bifida with neurological complications. Following pneumonia three months previously she had developed on each buttock a large indurated undermined ulcer which had defied all treatment. Swabs had always shown *Ps. pyocyanea*, and the sensitivity of this organism was 7 μg./ml. Under cover of systemic terramycin administration one ulcer was excised with success: the other healed under the influence of the drug.

A long-standing wound infection with *Ps. pyocyanea* (sensitivity 32 μg./ml.) was controlled by local application of a solution of strength 1,000 μg./ml., whilst a reasonable response was seen in the treatment by systemic means of a deep-seated ulcer with surrounding cellulitis situated in the natal cleft and infected with *Ps. pyocyanea* (sensitivity 15 μg./ml.) and *Bact. coli*.

Post-operative Infection

Four cases of post-operative complications were treated: one case of pneumonia with effusion following lobectomy for bronchiectasis (*Bact. friedländeri* and a pneumococcus), one of oesophageal abscess following oesphagoscopy (*Staph. aureus* and *Bact. coli*), one of post-operative peritonitis after hysterectomy (*Bact. coli* and *Str. faecalis*), and the last a case of pelvic cellulitis following vaginal hysterectomy (*Bact. coli*). All organisms were sensitive to less than 10 μg. of terramycin per ml.

The assessment of therapeutic effect on such cases is always difficult, as by the nature of the diseases other measures are employed concurrently. It can be said that all cases recovered completely, as fast as would be expected with the aid of efficient chemotherapy.

Miscellaneous Cases

Two patients with ulcerative colitis were treated. The first case, that of a man aged 39, had had long courses of streptomycin and chloramphenicol without benefit. A course of terramycin apparently produced great improvement, and he has remained well for three months after discharge.

The other case was not really suitable for assessment, as two months' hospital treatment had already caused a remission. Terramycin was administered in an attempt to clear his stools of blood, but without success.

One case each of dermatitis herpetiformis, Behcet's syndrome, and Reiter's syndrome, with arthritic involvement and joint effusion but with cessation of discharge, were treated with inconclusive or unsatisfactory results.

Toxic Symptoms

Of 33 patients who had courses of the drug lasting five or more days, 20 had no toxic symptoms. Thirteen patients, on direct questioning, admitted to feeling nauseated at times, usually at the beginning of the course; eight of these vomited one or more times. In the case of one very ill lady, vomiting was severe during the first 24 hours and the drug was stopped.

One case developed a sore throat, a severe substernal pressure sensation, and respiratory distress on the third day. The symptoms regressed 12 hours after the drug was stopped and further administration later did not reproduce this syndrome. No diagnosis was made of the cause of the symptoms, which may have been coincidental.

One old lady with very numerous disabilities developed an erythematous rash on the tenth day of treatment, and on the next day the Hess capillary test was very strongly positive. Two days later, while the normal faecal flora was still absent, the Hess test became normal. In her case all blood studies were normal; patch and prick tests to the drug were negative. Subsequently a further five-day course of terramycin was administered; the rash did not recur and the Hess test remained negative.

On the second and third days of treatment nine cases developed transient looseness of bowels; in three cases this was of moderate severity, but in none was it necessary to stop the drug.

In view of the profound changes in bacterial flora produced by the drug, a watch was kept for possible signs of vitamin deficiency: none was seen. It was felt that the case which developed the positive Hess test could not be regarded as one of vitamin deficiency, since the increased capillary fragility returned to normal whilst the usual bacterial flora of the bowel was still absent.

We noted that, as with aureomycin, the incidence of gastro-intestinal upset was greatly reduced by administering the drug with milk, and we were able to show that this procedure exerted no detectable effect upon the serum levels. It is perhaps of interest to state that with the one case in which the drug had to be discontinued owing to vomiting no milk was given.

Though the incidence of gastro-intestinal upset reported here is considerable, we used doses at the upper end of the scale, and with the exception of one case were able to continue with the drug. In three cases, however, in which vomiting occurred several times, very low serum and urine levels were recorded, which suggested that the oral route in these patients was unsatisfactory.

A suitable preparation of the drug for intravenous use has now been developed; this is claimed to be well tolerated and to circumvent gastro-intestinal symptoms in susceptible patients.

Conclusions

Our clinical experience has shown terramycin to be an antibiotic of low toxicity which is readily absorbed from the gut and which rises to satisfactory levels in serum, urine, faeces, and probably in most serous cavities. It is unfortunate that the blood–brain barrier is penetrated only poorly, but, as experience with other antibiotics has shown, this is not necessarily a bar to the efficient treatment of meningeal infections.

Our limited clinical results bear out expectations founded on the *in vitro* activity of the drug.

We would draw particular attention to the high levels of the drug in the urine and to our observations that the urinary *p*H seems to be immaterial in procuring successful results. The table of bacterial sensitivities shows that all the common urinary pathogens, with the exception of *Pr. vulgaris* and some strains of *Ps. pyocyanea*, are sensitive to concentrations many times less than those obtained therapeutically. It appears likely that with high dosage, leading to urinary levels of 300–400 μg./ml., practically all cases infected with *Ps. pyocyanea* will be amenable to therapy. Further, the fact that a number of strains of *Pr. vulgaris* are sensitive to chloramphenicol and streptomycin means that we now have efficient agents for the treatment of nearly all urinary bacterial infections.

In addition to our findings with the treatment of *Ps. pyocyanea* infections of the urinary tract, our preliminary data with regard to superficial infections with this organism show that terramycin offers real promise in controlling pyocyanea infections by local or systemic administration.

The striking changes in bacterial flora produced by terramycin and the high residual concentrations in the faeces will still further increase the scope and safety of gastro-intestinal surgery and enhance the medical management of intestinal infections.

We have noted in several cases that terramycin has produced clearing of abnormal nasal flora and considerable change in the bacterial content of sputum in cases of bronchiectasis; these findings indicate additional therapeutic uses.

We have not yet observed any striking difference in antibacterial activity between terramycin and aureomycin, with the one exception of *Ps. pyocyanea*, against which terramycin is more effective. Terramycin is also much more stable in solution than aureomycin, which is particularly advantageous in laboratory work.

We wish to express our grateful thanks to Professor Sir Alexander Fleming for much advice in these investigations and for enabling us to obtain supplies of terramycin, generously provided by Messrs. Chas. Pfizer and Co., of New York. We acknowledge the help and advice of Professor Robert Cruickshank and the valuable technical assistance of Mr. D. Stratful in the routine laboratory work. We also wish to thank the members of the consultant staff of St. Mary's Hospital for granting us access to the cases described.

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SUPRANUCLEAR BULBAR PALSY (PSEUDOBULBAR PALSY) IN MITRAL STENOSIS

BY

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During the latter half of last century reports of cases referred to as "labio-glosso-pharyngeal palsy" began to appear in the English, French, and German literature. They were a heterogeneous group and included both the form now known as progressive bulbar palsy and other varieties in which bulbar palsy had been produced by bilateral lesions confined to the cerebral hemispheres. Oppenheim and Siemerling (1886) first attempted to differentiate between these groups, which they described as true bulbar paralysis and pseudobulbar paralysis. They added a description of the emotional lability which led to the latter condition being sometimes called "the laughing sickness."

The term "pseudobulbar palsy" has long been recognized as being unsatisfactory. Tilney and Morrison (1912) criticized it as giving no indication of either the site of the lesion or the nature of the disease. The synonym "supranuclear bulbar palsy." is more accurate, but "notwithstanding this," as Tilney and Morrison then commented, "pseudobulbar palsy, although a purely conventional term, has gained a fixed place in the literature." The traditional title dies hard and unfortunately has still not been displaced by the more appropriate and descriptive name of supranuclear bulbar palsy. The occasional combination of nuclear and supranuclear lesions shows how further confusion may arise if the terms "true" and "pseudo" are retained.

It is unnecessary to give an account here of the distinctive clinical features of supranuclear bulbar palsy, as they are fully described elsewhere. Oppenheim's (1911) early account is of interest, and good recent descriptions have been given by Langworthy and Hesser (1940), Alpers (1946), and Wechsler (1947). Kinnier Wilson (1924) has discussed the interesting related problem of pathological laughing and crying.

Supranuclear bulbar palsy most commonly results from arteriosclerosis which has produced bilateral areas of cerebral softening. In many cases, therefore, there is a history of an attack of weakness on one side of the body, followed later by an attack on the other side, the bulbar symptoms developing acutely after the second attack. In its sudden onset, its frequent association with double hemiplegia, its irregular non-progressive course, its lack of lower motor neurone involvement, and in its associated disturbance of emotional control, supranuclear or pseudobulbar palsy is distinct from progressive bulbar palsy (in which local bulbar involvement may be part of motor neurone disease). Supranuclear bulbar palsy may occasionally occur in the course of other pathological conditions (such as disseminated sclerosis, cerebral metastases, or agenesis) in which there are scattered bilateral lesions involving the corticobulbar tracts. It is a clinical syndrome and not a disease entity.

Several of the early descriptions of what we now regard as supranuclear bulbar palsy referred to young or middle-aged subjects with bilateral cerebral thromboses, probably of syphilitic origin. Two cases produced by cerebral embolism, however, were described by writers in the last century. Barlow (1877) published the clinical and post-mortem findings in "a case of double hemiplegia with symmetrical lesions." This referred to a boy, aged 10, with congenital heart disease and infective endocarditis. First a left and then a right cerebral embolism occurred, after which he developed the characteristic features of supranuclear bulbar palsy, including both emotional lability and urinary incontinence. Kirchhoff (1881) described the case of a man, aged 24, with mitral stenosis, who apparently developed bulbar paralysis from bilateral cerebral embolism. This resulted in drawling speech, dribbling of saliva, an almost immobile tongue, and bilateral facial weakness.

There seem to have been no further accounts of supranuclear bulbar palsy resulting from bilateral cerebral embolism, and we have been unable to find any modern reports of the condition occurring in rheumatic heart disease. Recently, however, we have seen three cases of mitral stenosis in which well-marked supranuclear bulbar paralysis was apparently produced by successive cerebral emboli. It may therefore be of interest to place the following examples on record.

Case 1

A trained nurse aged 47 was admitted to the Royal Northern Hospital on January 5, 1950. She had had rheumatic fever and chorea in childhood and heart trouble since then. She was known to have been in hospital in recent years with mitral stenosis and auricular fibrillation, and her pulse had remained irregular. She had felt well that afternoon, but on stretching to close a window she suddenly became faint and dizzy. She did not lose consciousness, but developed a headache and vomited. The left side of her face and the left upper and lower limbs seemed numb and she had difficulty in using her left arm.

On examination she was alert and her speech normal. Auricular fibrillation was present, with a pulse rate of 70 a minute and a systolic blood pressure of 120 mm. Hg. A diastolic and a systolic murmur were heard at the mitral area. Optic disks were normal. Detailed examination of the central nervous system was made next morning, when, apart from slight weakness of flexion of the left hip, there were no significant motor, sensory, or reflex abnormalities of the limbs. The only other development was weakness of the internal rectus muscle of each eye. It was thought that her attack was the result of a transient right-sided cerebral embolism, and that the subsequent ocular signs were probably the result of another small embolus involving part of the mid-brain.

During the night of January 8 she had another attack. Her pulse rate fell to 40 a minute and she appeared faint and confused. Next morning she was found to have a right hemiparesis with upper motor neurone type of weakness of face and limbs. A further cerebral embolism, this time involving the left side of the brain, had presumably occurred.

After this episode the whole clinical picture changed and she presented the characteristic appearance of a patient with supranuclear bulbar palsy. Her speech was rapid, spastic, and indistinct, and she had difficulty in swallowing and coughing. The tongue was spastic. She showed gross emotional lability, bursting into either tears or laughter without adequate cause. She became incontinent of faeces and urine. At this stage she had a pronounced jaw-jerk and a bilateral extensor plantar response. There was no sensory impairment. Lumbar puncture on January 11 showed normal cerebrospinal fluid (C.S.F.). The Wassermann reaction and Lange curve were negative.

The power of the right side of the body began to improve within two days and sphincter control was regained in two weeks. After about four weeks she was beginning to get about and walked with the short spastic steps reminiscent of the double hemiplegia of cerebral arteriosclerosis. The defective ocular movements had by this time almost gone. The spastic dysarthria and emotional lability improved gradually. When last seen, at the end of February, she no longer wept or laughed involuntarily, but still smiled and laughed in a slightly spastic fashion and with little retraction of the angles of her mouth. Some weakness of flexion of the hips, especially the right, persisted, and, though her walking had improved, she still took short spastic steps on a rather wide base. Her auricular fibrillation was unaltered. She felt well and was discharged to convalescence.

Case 2

A man aged 32 was referred to the neurological clinic of the Mid-Herts Hospital on October 20, 1949, for speech therapy. He had had rheumatic fever when aged 9, and since then was known to have had mitral stenosis. At the age of 29 he had had an attack of cardiac asthma.

He said that 18 months ago he had suddenly lost consciousness at 6.30 one morning. His wife had noticed jerking movements of his hands at the time. He recovered his senses by about 9 a.m., and then found that the right side of his face and the right upper limb were paralysed and the right lower limb was weak. He was drowsy, aphasic for a few days, and incontinent of urine. The hemiparesis and speech defect improved, and after about two weeks he noticed only clumsiness of the right hand.

Three weeks after this episode he had another attack in the early morning. His pulse was said to have been slow and irregular at the time. He developed sudden weakness of the whole of the left side of the body but did not lose consciousness. He became completely anarthric, his tongue was stiff and immobile, and he could not cough voluntarily. There was dysphagia with nasal regurgitation of liquids and dribbling of saliva. Incontinence of urine was followed by precipitancy and increased frequency. The left hemiparesis and the dysphagia improved during the next few weeks. He became able to speak in a whisper after three months and in a feeble voice after five months.

When seen in October, 1949, he noticed residual weakness on the left side and was subject to occasional involuntary flexion spasms of the left leg. He still had a little difficulty in chewing and swallowing, and said that his tongue felt stiff. Urgency of micturition persisted. His wife said that he had become easily tearful and irritable.

On examination he was alert but slightly emotional. There was no dysphagia, but he spoke in almost a whisper, with his teeth hardly separated. His speech was spastic, indistinct, and tended to accelerate. There was also a tendency to diminuendo repetition of the end of a sentence (palilalia). There was some bilateral weakness of the lower part of the face, although emotional movements were overactive. Eye movements and optic disks were normal. His tongue moved slowly and stiffly. A brisk jaw-jerk was obtained. All his limbs were slightly hypertonic and his movements slow. Power was slightly impaired on the left side and he walked slowly, dragging his left foot. Sensation was normal. The arm reflexes were brisk and equal and finger-jerks were obtained. The knee-jerks and ankle-jerks were also brisk, particularly on the left side. Abdominal reflexes were feeble. The right plantar response was equivocal and the left extensor. His pulse rate was 80 a minute and the rhythm regular. His blood pressure was 120/80 mm. Hg. The heart was slightly enlarged; a loud systolic and a mid-diastolic murmur were heard at the apex, and the pulmonary second sound was accentuated. On subsequent examinations, however, auricular fibrillation was sometimes present.

He was last seen some nine months later, when no further change was evident.

Case 3

A woman aged 20 was admitted semi-conscious to St. Thomas's Hospital on August 9, 1949. She had had chorea when aged 11 years and had begun to be easily breathless at 16. She had been attending the out-patient department since the age of 18 on account of rheumatic heart disease, and had signs of mitral stenosis with normal cardiac rhythm. During the two years that she continued under observation as an out-patient she was troubled by several attacks of nocturnal dyspnoea. She was of poor intelligence, but there were no other abnormal findings and her pulse had remained regular. When seen on the morning of August 9 no change in her physical signs was noted. That afternoon, however, her left hand and arm began to shake. Her husband said that she laughed and then suddenly fell unconscious in her chair. Her left arm appeared limp. She was brought into hospital about one and a half hours later.

On admission she was stuporous but reacted to painful stimuli. Her pulse rate was 70 and the rhythm regular. Eye movements, pupils, and optic disks were normal. Her lower jaw tended to hang open and the limbs were flaccid. The tendon reflexes were brisk and equal, and both plantar responses were extensor. The C.S.F. was entirely normal. The next day she was more conscious. She was dysphasic, but said a few words in a spastic and indistinct fashion. She was liable to outbursts of uncontrollable weeping and laughter and often made loud spastic cries for no good reason. She was incontinent of urine. Slight right facial weakness of upper motor neurone type was evident and there was some defect in conjugate deviation of the eyes to the right. Her palate moved poorly and she had difficulty in swallowing. On trying to drink she would dribble fluid from her mouth and sometimes through her nose. Power in the limbs was diminished, particularly on the left side, and she had to be fed. The tendon reflexes were brisker on the left side than on the right. The abdominal reflexes were absent, and both plantar responses were extensor.

During the next few days the power in her left side improved and she regained control of her bladder. Her speech, which was at first almost unintelligible, improved more slowly. She continued to show pronounced emotional lability and would laugh and cry in a spastic fashion for little or no cause. She got up after about two weeks and was discharged a week later. She then talked and walked fairly well. Both plantar responses remained extensor.

Though much improved when last seen, six months later, she was still easily moved to spastic laughter or tears and spoke with a nasal dysarthria. Her soft palate moved poorly and there was occasional slight dysphagia. Eye movements were normal. There was a residual right facial weakness. The tone of the limbs was normal. The left upper limb was slightly weaker than the right and there was some weakness of flexion of both thighs. She was unable to use her hands normally but she walked without difficulty. The tendon reflexes were brisk, more so on the left side than on the right. The plantar responses were equivocal and attempts to elicit them made her weep. She had full control of her bladder. There had been no further symptoms directly referable to the cardiovascular system.

Discussion

Each of these patients had a previous rheumatic history. All three had mitral stenosis and two of them showed auricular fibrillation.

In Case 1 the history suggested the occurrence of several emboli in the course of three to four days. First the right and then the left side of the brain was involved. With the development of the bilateral cerebral lesions the picture changed to that of a supranuclear bulbar palsy, uncontrolled laughing and crying being a prominent feature. Within two months the emotional symptoms had almost completely disappeared, though some spasticity of speech and gait remained

Case 2 also had two acute cerebral attacks: the first resulted in a right hemiparesis, and the second, three weeks later, in a left hemiparesis. Supranuclear bulbar palsy developed with the second attack and disturbance of articulation was the most striking feature.

In Case 3 it seems likely that several small cerebral emboli affected both sides of the brain almost simultaneously. Typical supranuclear bulbar palsy immediately resulted and the spastic laughter and tears were very evident. Although emotional control improved considerably it was not complete six months later.

All three cases had marked dysarthria and dysphagia and all were temporarily incontinent of urine. The onset of supranuclear bulbar palsy was in each case abrupt, but all three showed considerable improvement.

In supranuclear bulbar palsy resulting from cerebral arteriosclerosis the vascular degenerative changes are likely to be diffuse and multiple. Bilateral pyramidal-tract signs are usually present and there may be a history of double hemiplegia, though there is often an interval of months or years between the involvement of the two sides. Sometimes the supranuclear bulbar features are accompanied by only a hemiplegia or hemiparesis. More rarely there is no limb paralysis at all, though the plantar responses may be extensor. In addition to the involuntary laughter and crying, progressive dementia is seen in the arteriopathic group and occasional extrapyramidal features have been described. The course of the disease is irregular and may be prolonged.

When supranuclear bulbar palsy is produced by bilateral cerebral embolism, however, there is usually a history suggesting sudden vascular occlusion on one side of the brain, followed quite rapidly by the same process on the opposite side, so that bilateral interference with the cortico-bulbar and cortico-spinal pathways immediately results. The embolic form of supranuclear bulbar palsy may occur in young subjects. Dementia is not a feature of the condition, and, if the emboli are small, rapid resolution of symptoms may occur.

Summary

Supranuclear bulbar palsy (so-called pseudobulbar palsy) most often results from diffuse cerebral arteriosclerosis, with or without a history of double—that is, bilateral—hemiplegia.

Three cases of mitral stenosis are described in which bilateral cerebral emboli resulted in the abrupt development of the characteristic syndrome of supranuclear bulbar palsy with bilateral pyramidal-tract signs.

We should like to express our thanks to Professor E. P. Sharpey-Schafer, Dr. J. W. Aldren Turner, and Dr. E. D. Mackworth for permission to describe these cases, originally admitted to hospital under their care.

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Dr. L. Leslie has been made vice-chairman of the Berkshire Executive Council in place of the late Dr. J. McCrea.

MORTALITY IN GERIATRIC SURGERY*

BY

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The life-span has been increasing markedly, as is shown by Chart 1. According to the National Office of Vital Statistics (1950), it is 67.2 years in the United States. Chart 2 indicates that those aged 65 and over constitute 7.6% of the population. The Royal Commission on Population (1949) reports that in 1947, in Great Britain, those who were 60 years and over constituted 15% of the population.

More attention is being focused on problems of ageing. It is our function to apply our art not only to save life but to add years to life and life to years, and to reduce mortality. The surgeon has come to play a most important part in the attainment of these goals. We have had an unusual opportunity for the practice of geriatric surgery at the Goldwater Memorial Hospital, in New York City. This 1,500-bed municipal hospital was opened in 1939 for the care and study of chronic disease. Most of the patients are old and are substandard risks. They are afflicted with chronic and degenerative diseases and with nutritional deficiencies. Nevertheless, we do not hesitate to meet surgical indications if there is a chance to save life or to prevent invalidism.

Only patients over the age of 60 are included in this report. Table I (Carp, 1946) shows comparative operative mortality statistics from a number of clinics. At our clinic, from 1939 to 1944, the mortality rate in 450 major

TABLE I.—*Comparative Operative Mortality Statistics (Carp, 1946)*

Source	Age Groups	No. of Major Operations			Mortality %		
		M.	F.	Total	M.	F.	Average
Goldwater Memorial Hospital*, 1939–44	61–70	152	50	202	15·78	22·0	18·89
	71–80	148	47	195	24·18	27·6	25·89
	81–90	38	12	50	44·73	25·0	34·86
	91–100		2	2			
	101–110		1	1			
	Total	338	112	450			22·66
Bailey (1934) ..	60–84			185			7·6
Parsons and Purks (1942)	60 and over			100			17·0
Clagett (1943) ..	60 ,, ,,			1,204			9·0
Hay (1940) ...	70 ,, ,,			536			16·6
Evans and Key (1942)	60 ,, ,,			83			7·2
		Grand total		2,558	Grand aver.		13·1

* The emergency operations were 12·88% of the total number.

TABLE II.—*Goldwater Memorial Hospital: Major Operations on Substandard Risk Patients Over 60 Years of Age. Post-operative Mortality Rates Within 30 Days*

Period	No. of Major Operations		% Emergency of Total	Post-operative Deaths Within 30 Days		% Mortality Rate	
	Total	Emergency		Total	Emergency	Total	Emergency
1945 ..	166	32	19·4	40	23	24·1	71·9
1946 ..	131	32	24·4	25	16	19·1	50·0
1947 ..	162	44	27·2	23	12	14·2	27·3
1948 ..	193	41	21·2	25	11	12·9	26·8
1949 ...	199	56	28·1	34	18	17·1	32·1
1945–9 ..	851	205	24·1	147	80	17·3	39·0
1939–44 ..	450	59	13·0	102	26	22·6	44·0

*Read before the Section of Geriatrics at the Annual Meeting of the British Medical Association, Liverpool, 1950.

TABLE III.—*Analysis of Causes of Death in 100 Consecutive Necropsy Protocols in Patients Over 60 Years of Age Who Died Within One Month After Operation (Carp, 1948)*

	Principal Causes	Important Contributory Causes
Bronchopneumonia	28	10
Cardiac dilatation	27	3
Peritonitis	18	1
Thrombosis and embolism	7	2
Sepsis	7	1
Pyelonephritis	6	15
Coronary occlusion	3	2
Anaesthesia	2	—
Lung abscess	1	—
Metastatic carcinoma	1	12
Decubitus ulcers	—	5
Pulmonary tuberculosis	—	3
Bronchiectasis	—	2
	100	

operations, 13% of which were emergency cases, was 23%. During 1945–9 the mortality rate in 851 major operations (Table II) has been reduced to 17%, with the emergencies constituting 24%. There is also a 5% drop in mortalities from emergency surgery when the years 1939–44 are compared with the years 1945–9. Table III (Carp, 1948) shows that the major causes of death in 100 consecutive necropsies on patients over 60 who died within one month after operations were bronchopneumonia, heart failure, and peritonitis. The major contributory causes were pyelonephritis and metastatic carcinoma.

Some Common Problems

Disease in the aged may be complex, varied, and confusing, contributing to diagnostic error and presenting problems in treatment.

Emergency Surgery.—This produces an inordinately high mortality rate. It is about two and a quarter times that of elective surgery. Cutler's (1947) figures from our service showed that among patients whose average age was 74 years there were 84 deaths following 188 emergency operations — a mortality rate of 44%. If no attempt at surgical relief had been made nearly all these patients would have died. Recent mortality in emergency cases is 32% (Table II). The risk is greater when patients come to operation late, especially in cases of spreading infections and obstruction in various systems. Deterioration is then very rapid. Valuable time may be lost because differential diagnosis is difficult; pre-operative preparation may be prolonged; the patients are considered "too sick or too old"; and hope for improvement is too long entertained. If the mortality in acute cases is to be reduced there must be quick supportive therapy, with the earliest and simplest operation to effect relief and measures to prevent post-operative complications.

Early Cholecystostomy.—This is the operation of choice for acute cholecystitis and/or cholelithiasis. The patients in this group were desperately ill. Old people are especially susceptible to sudden gall-bladder catastrophes. The largest

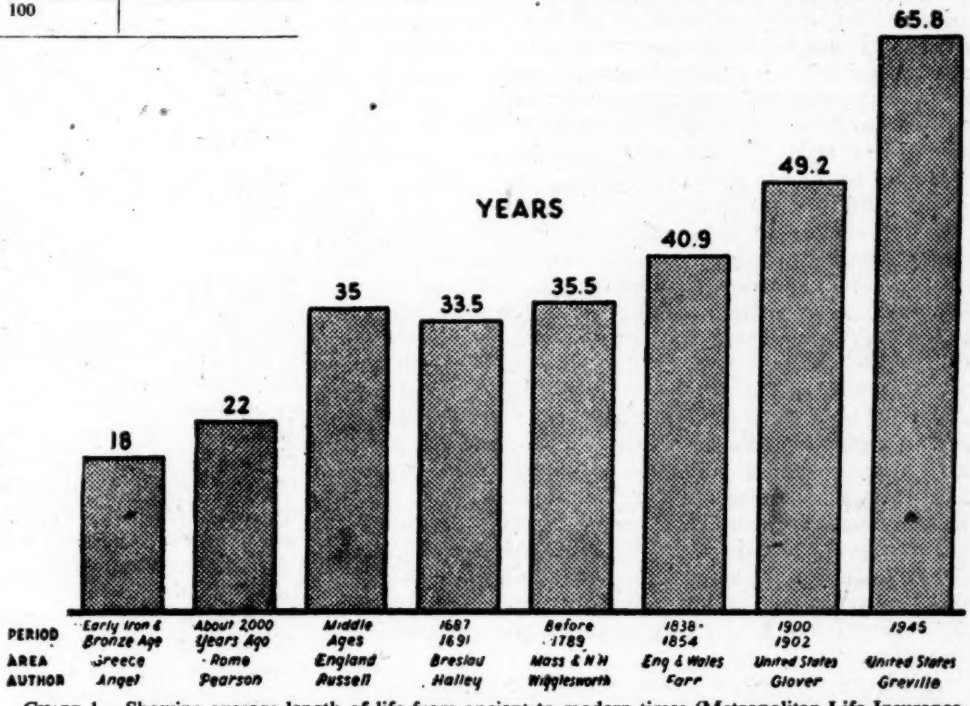

CHART 1.—Showing average length of life from ancient to modern times (Metropolitan Life Insurance Company, 1947).

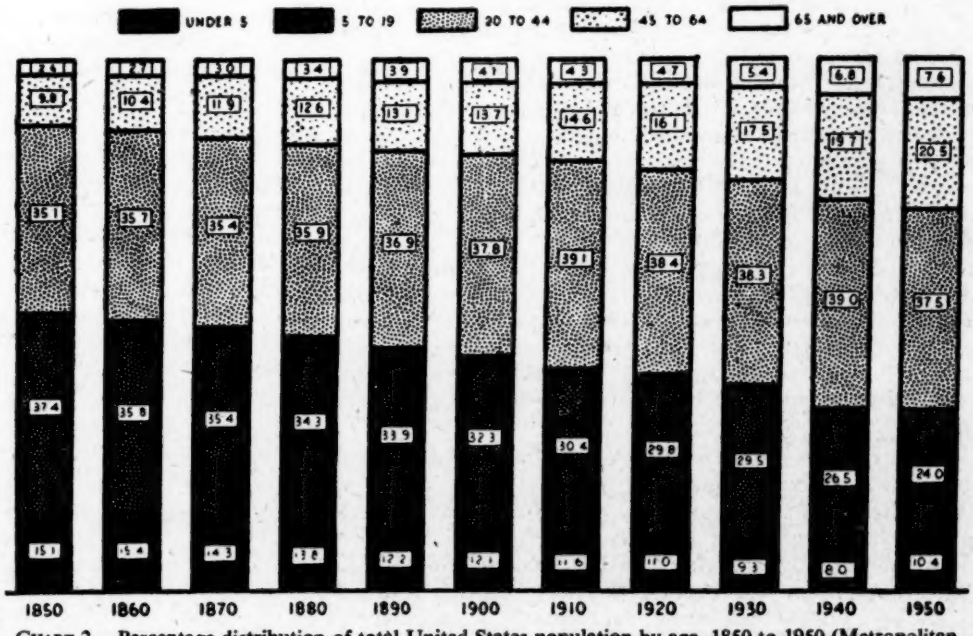

CHART 2.—Percentage distribution of total United States population by age, 1850 to 1950 (Metropolitan Life Insurance Company, 1949). 1850 to 1940 from U.S. Census data; 1950 estimates published by Bureau of the Census, 1949.

percentage of gall-stones are found in the sixth and seventh decades (Jaffé, 1933). Rosenthal (1944) showed that of 300 routine necropsies at the Goldwater Memorial Hospital on patients between the ages of 60 and 100, 23% of 133 men and 40% of 87 women had diseased gall-bladders with stones. At first, cholecystostomy was the operation of choice. However, with improvement in anaesthesia, and with supportive and antibiotic therapy, and influenced by the propaganda for cholecystectomy, we undertook this procedure instead. Almost 50% mortality ensued from pneumonia, heart failure, or peritonitis. Cutler (1949) reported from our service 34 acute cases, whose average age was 73 years. He concluded that such cases should come to surgery as soon as is consistent with adequate preparation, and he recommended cholecystostomy as the safer emergency procedure. With the readoption of cholecystostomy the nine succeeding cases (average age 79.3 years) showed a mortality of 22%. In common-duct obstruction by stone, cholecystostomy is done if a free flow of bile results. If subsequent indications arise a patient is then in better condition to withstand cholecystectomy or choledocotomy.

Intestinal Obstruction.—This calls for immediate tube decompression, for methods to increase blood volume and to restore fluid and electrolyte balance, and for quick operative relief. In treating intestinal obstruction there has been a tendency to prolong the use of tube decompression. Clinical results have convinced us that in the aged such a policy will lead to a mortality of 60%. Surgical relief within 24 hours cuts mortality to 39%. Cutler (1950) has supplied these figures after a study of 120 cases. A patient may improve rapidly with tube decompression and parenteral therapy, encouraging postponement of surgery. Undue postponement will turn the tide against him. Location of the obstruction can be aided by rapid *x*-ray examination. Relief of the obstruction by the simplest appropriate procedure is indicated. More radical therapy, if required, can be undertaken at a later date when the patient is in better condition.

Acute Appendicitis.—This is a difficult diagnostic problem and its mortality is high. Frequently the clinical picture of appendicitis in the aged is confused and the history and physical signs are atypical. Patients, as a rule, come to operation too late. Accompanying disease and diminished resistance to infection increase the incidence of gangrene and perforation, and raise the post-operative morbidity and mortality (Darling and McIver, 1950). We have had 26 patients of over 60 diagnosed as suffering from acute appendicitis. The mortality rate in 19 proved cases was 36%. In another six patients (23%) the diagnosis was incorrect. In three of these no accountable pathology was found, one had a carcinoma of the caecum, one had a fibrotic appendix, and one had a calculous pyonephrosis. The average age of the proved cases was 75 years. Ten of the appendices perforated. At the four necropsies among the seven patients who died the causes of death were found to be pneumonia and cardiac failure in one case, general peritonitis in two cases, and shock in the other.

Hernia.—Surgical therapy under local analgesia is advisable for symptom-producing inguinal and femoral hernia. When hernia is accompanied by pain, a disabling mass, or recurrent incarceration, operative relief, especially under local analgesia, is gratifying. Patients walk within 24 hours after operation. Strenger (1949) has reported from our clinic on 95 operations for hernia, including 78 inguinal and 10 femoral. Three patients died after emergency surgery for strangulation. One elective case died of brain tumour. There were no fatalities in 44 additional cases. The patients' average age was 71 years. Four of them had strangulation, but in no case was resection necessary.

Tourniquets.—The use of the tourniquet for amputations is not approved. We hold that the trauma of tourniquet constriction will further damage affected blood vessels. We have abandoned its use in the past three years. Previously, 15 patients had mid-thigh amputations for arteriosclerotic gangrene under crymo-anaesthesia (refrigeration) with tourniquet. All the stumps were closed and eight of them broke down. Five patients died. In three of these there was found massive thrombosis in large blood vessels in the abdomen or thorax. We believe that the tourniquet was the main predisposing factor in thrombosis and stump breakdown. While preparing the patient for amputation, however, the tourniquet is useful in limiting the swift ascent of infection in acute cellulitis.

Mid-thigh Amputation Stumps.—Closure of mid-thigh amputation stumps in layers is advisable for diabetic or arteriosclerotic gangrene, except when ascending infection is present or when the circulation of the amputation site is seriously impaired. The practice of leaving stumps open does not seem justified. Wounds take much longer to heal, asepsis and nitrogen balance are difficult to maintain, and the stump may be unsatisfactory. Unless there is ascending infection or thrombosis of the femoral vessels we close muscle, fascia, and skin, with the free use of antibiotics. Sixty patients (average age 68) had closure of stumps. Of these, 23 had diabetic and 37 arteriosclerotic gangrene. In 20 of the diabetic patients (87%) the stumps healed nicely. In 22 of the arteriosclerotic patients (60%) there was good union. Four other patients in this group had delayed union. Of the 15 patients in both groups who had crymo-anaesthesia with tourniquet, eight (53%) had wound breakdown. We believe that factors in the breakdown were the anoxia and the thermal injury to the tissues. In 16 patients (average age 72) stumps were left open and traction was applied. In 75% the indication was ascending infection. The average healing-time in the 11 patients who survived was 50 days.

Suggested conclusions are : (1) the interdiction of the tourniquet and crymo-anaesthesia, except in sepsis and swift ascending infection ; (2) careful haemostasis ; (3) traction on stumps which are left open ; and (4) early and frequent wound inspection to detect infection.

Decubitus Ulcers.—Prophylactic care will minimize the incidence of decubitus ulcers. The factors in the physical decline that accompanies decubitus ulcers are toxic absorption, sepsis, and nitrogen loss. Decubitus ulcers were the contributory cause of death in 5% of our necropsies. Maintenance of a positive nitrogen balance, the relief of local pressure, early ambulation, repeated change of position, cleanliness, skilful nursing, and keeping the skin dry constitute the best treatment. We have tried operative closure of some of the decubitus ulcers without success.

Ambulation.—Early out-of-bed care and ambulation are beneficial. Early ambulation is indicated in the old patient. It induces better breathing, appetite, and urinary and bowel function. It seems to reduce the incidence of pneumonia, heart failure, thrombosis and embolism, and decubitus ulcers.

Chemical Balance

Adequate chemical balance helps to maintain comparatively normal homoeostasis and physical reserve. In the

aged, physical deterioration is accompanied by rapid and marked chemical imbalance. Our principles for supportive therapy are :

1. Food is preferable to parenteral therapy. A high-calorie, high-protein, and vitamin-rich diet is important. The edentulous should be given cooked ground meat.

2. The daily water requirement of 2.5 litres may have to be doubled, with additional sodium chloride, in patients who have been dehydrated.

3. The daily requirement of 1 g. of protein per kilogram of weight may have to be doubled or trebled after operation, or in depleting diseases or infection.

4. Starvation produces both nitrogen and potassium loss. Low blood potassium may produce asthenia, flaccid paralysis, respiratory distress, and ileus. Bodansky (1950) gives potassium as beef broth or meat juices, or potassium chloride, 2–4 g. daily. Randall *et al.* (1949) recommend a mixture of 1 g. each of potassium acetate, bicarbonate, and citrate in 8 ml. of water: 4 ml. may be taken three times daily. For intravenous use, 2–4 10-ml. ampoules of 15% potassium chloride may be given in 24 hours. Repeated blood potassium determinations are required.

5. Patients with diminished cardiac reserve tolerate best a hypodermoclysis of 2.5% glucose in 0.45% solution of sodium chloride. If diuresis is poor, 50–100 ml. of hypertonic (25–50%) dextrose solution intravenously is recommended.

6. In alkalosis Bodansky (1950) has used a 2% ammonium chloride solution intravenously.

7. A controlled diet and insulin are indicated for the diabetic. In emergencies 5% glucose in saline intravenously, with one unit of insulin for each 2 g. of carbohydrate, is recommended.

Other Problems

Heart Disease.—An ageing heart, coronary sclerosis with myocardial fibrosis, and valvular defects do not necessarily contraindicate operation. Pre-operative digitalization is advisable unless there is a definite contraindication. In 100 necropsies, 27% of the post-operative deaths were found to be caused by heart failure and 3% by coronary occlusion. All the necropsies revealed varying degrees and types of cardiac pathology. Master *et al.* (1950) have stated that "patients with severe heart disease tolerate even major operations if adequate precautions are taken to avoid anoxaemia and coronary insufficiency." Our experience supports these observations. We have used digitalis to strengthen the myocardium, unless there was a contraindication. Irregular cardiac action on the operating table can be controlled by the intravenous use of 5 ml. of a 1 or 2% solution of procaine for ventricular arrhythmias or auricular tachycardia; oxygen and digitalis for interference in the conduction system; intravenous quinidine for ventricular fibrillations; and adrenaline and cardiac massage for cardiac arrest (Collins, 1950).

Anaesthesia.—Improvement in anaesthesia is a major factor in the increasing success achieved by geriatric surgery. Recent advances in anaesthesiology have contributed to reduce morbidity and mortality. Anaesthetists plan the anaesthesia for the individual patient and supply supportive therapy during operation. Pre-operative sedation should be minimal. Cyclopropane is the preferable general anaesthetic. Intravenous sodium thiopentone is favoured for short anaesthesias, with curare as an adjunct for long procedures. Local analgesia, without adrenaline, is very useful in selected cases. Intratracheal anaesthesia is used in thoracic and some oral surgery, and in prolonged upper abdominal surgery. Our service has had but one anaesthetic death in ten years.

Psychological Approach.—Sick old people respond to kindness and understanding. A frank, tactful, and optimistic manner, patience, and kindness will help understanding and inspire confidence. They can convert an uncooperative or frightened patient to a more reasonable and hopeful frame of mind. Ministers in the various religious groups have been most helpful. A proper psychological approach can mean the difference between co-operation and a will to live, and frustration and a hope to die.

Summary

With scientific advance, improved techniques and anaesthesia, and better understanding of the degenerative processes accompanying old age, it is possible for geriatric surgery to provide more comfort in disabling diseases and to prolong life when it is threatened.

Our mortality statistics show a decline (5%) in elective and emergency surgery when the years 1939–44 are compared with 1945–9.

In emergency surgery the mortality rate will be from two to two and a quarter times that of elective surgery.

Our clinical and necropsy experience has pointed to methods of reducing mortality. Some of them are briefly discussed.

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THERMAL COAGULABILITY OF SERUM PROTEINS AND THE DIAGNOSIS OF MALIGNANT DISEASE

BY

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The publication from a reputable source of any laboratory test which may be of value in the diagnosis of malignant disease is a matter to be examined seriously.

Huggins *et al.* (1949) published the results of their investigations on the altered thermal coagulability of serum proteins in malignant disease. They described a test involving the use of iodoacetic acid which was said to increase the sensitivity of the discrimination between the sera of patients with malignant disease and those of healthy individuals and subjects with non-cancerous diseases. While these authors stated that the deficiency revealed in the serum in malignant disease was not specific, and that similar results were obtained in pulmonary tuberculosis and some acute inflammatory processes, their results were striking enough to demand further investigation. Some other groups of American workers have recently described their experience with this test. A series of tests was carried out at the Christie Hospital during the last year, the results of which are given below.

The iodoacetate test consists in exposing a given concentration of serum to increasing concentrations of iodoacetate in buffer at *p*H 7.4 and heating to 100° C. for 30 minutes. Iodoacetic acid reacts with certain linkages in the protein molecules and interferes with the coagulative process which normally occurs on heating. The end-point is found by estimating in which of the series of tubes the contents have just failed to remain fluid, and the quantity of iodoacetic acid thus required is related to the amount of protein present in the serum as an "iodoacetate index." Huggins and his co-workers at first described a certain technique; from this they later evolved a modified test in which the estimation of the end-point did not depend so much upon the personal opinion of the observer.

A trial of this later method (55 cases) convinced us that it was unreliable, and so in most of our tests their original technique has been used.

Blood for the tests was run into sterile tubes, allowed to clot for an hour or so, refrigerated overnight, and the serum removed aseptically and kept in the refrigerator for use. Each test was carried out in duplicate—the second test being made either concurrently or in the course of a few days. The interpretation of the end-point was made by one individual throughout, working entirely in ignorance of the origin of the serum. With few exceptions the duplicates gave reasonable correlation—either complete agreement or differing by one tube. The mean results were calculated when differences between duplicates occurred. In some tests the end-point was difficult to ascertain and in a few quite impossible (seven tests out of a total of 224). These latter occurred in individuals in whom the serum protein was high (8.2% or more) and the coagulation took place in floccules interspersed with clear fluid. The total serum proteins were calculated from the total nitrogen figures estimated by the micro-Kjeldahl technique.

All cases of malignant disease examined were new and untreated, and the pathology was confirmed histologically except in a few instances in which there was no doubt on clinical examination. No attempt has been made to relate the test to the clinical stage of the condition.

Results

The collected figures from our tests are shown in Table I and in histogram form in Fig. 1. In addition, a group of cases have been chosen to illustrate the relationship of the test to various clinical conditions (Table II). The distribution of the total serum proteins in the three groups—normal, malignant, and non-malignant pathology—is shown in Fig. 2. It is commonly stated that the serum proteins diminish in malignant disease, but in the individuals we have studied the general distribution pattern is normal.

TABLE I

	Normals		Non-malignant Pathology		Cancer	
	No. of Cases	Test +ve(%)	No. of Cases	Test +ve(%)	No. of Cases	Test +ve(%)
Huggins *et al.* (1949) ..	100	0	95	16	85	100
Bodansky and McInnes (1950)	68	0	68	6	137	26
Homburger *et al.* (1950)	47	27·5	108	70	102	93
Homburger (modified technique)	46	0	30	23	51	78
Cliffton (1949) ..	42	23	99	65	54	83
Jackson	38	26	63	80	61	64
Jackson (modified technique)	27	59	0	0	28	57

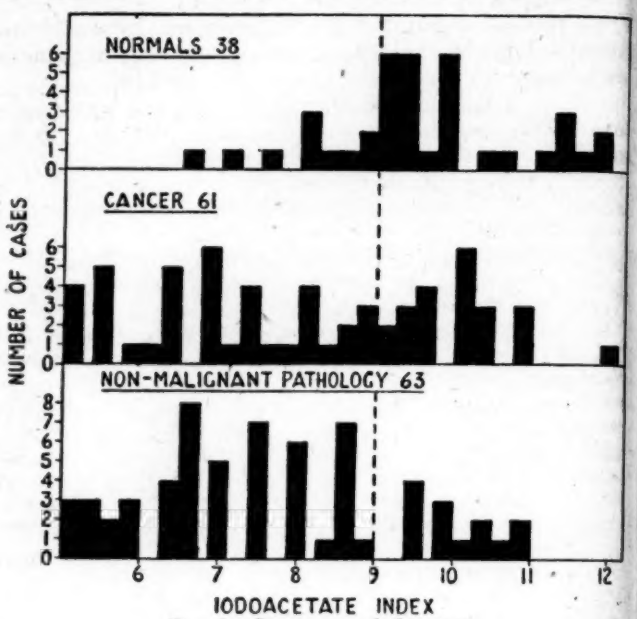

FIG. 1.—Serum coagulation test.

TABLE II

	Test Positive in
Carcinoma of tongue	3/5
Basal-cell carcinoma	1/6
Carcinoma of breast	4/11
Carcinoma of cervix	2/3
Leukaemias	6/7
Hodgkin's disease	3/4
Carcinoma of lung	8/9
Tuberculosis of lung	8/8
Pneumonias	10/10
Non-malignant pathology associated with haemorrhage	8/8
Total ..	53/71

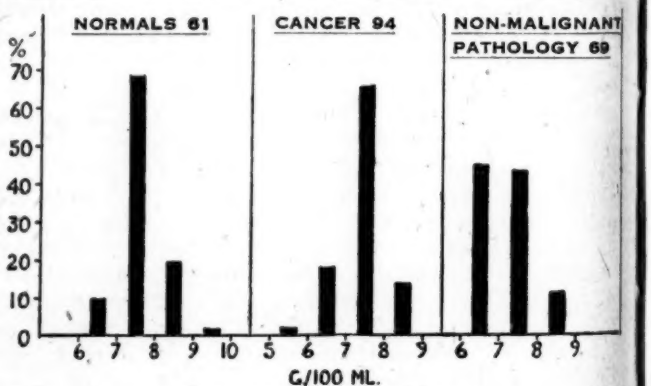

FIG. 2.—Total serum proteins.

Discussion of Results

Huggins *et al.* (1949) selected an iodoacetate index of 8.99* as a dividing-line between normal and abnormal. Not one of their series of 100 normal sera gave an index less than this figure. Of 85 cases of proved malignant disease all except three were found to have an index of less than 8.99. The three exceptions were patients with carcinoma under treatment, stated to be apparently well controlled. Of the group of non-malignant pathology, 16 out of 95 cases gave a "cancer positive" test (Table I). All these "false positives" were stated to have serious disease. No further information was given of the types of malignant disease tested or of the varieties of non-malignant pathology included in the group, except that there were seven cases of pulmonary tuberculosis, all of which gave a positive test.

*A difference in end-point of one tube makes an alteration of 1 unit in iodoacetate index.

Cliffton (1949) compared the results he obtained using three "cancer tests"—namely, an antiproteolytic reaction and thermal coagulation tests. Using the iodoacetate test, he found no significant difference in results whether the original technique of Huggins *et al.* or their later modification was applied. These results are shown in summarized form in Table I. In his entire series (235 cases) the overall accuracy in cancer diagnosis was only 55.5%.

Bodansky and McInnes (1950) found the original technique recommended by Huggins *et al.* unreliable and adopted their own modification of the second method described. Their results are summarized in Table I.

Homburger *et al.* (1950) published an account of their investigations and included a detailed list of cases. They used both techniques described by Huggins *et al.*, and, as we have done, made an attempt to assess the reliability and reproducibility of the test. They condemn the original method of Huggins *et al.*, maintaining that reproduction of the test by different investigators is impossible. They consider the modified method easier to reproduce and less complicated, but find the results so obtained at considerable variance with those from the former method (Table I).

Finally, Kiefer *et al.* (1950) carried out the modified technique of Huggins *et al.* on 700 apparently healthy men and women. All except six gave values higher than 9.3. These latter were found to give figures greater than 9 on repetition. Of 25 cancer cases run as controls, 76% gave a positive test. According to these workers "the thermal coagulation end-point is striking and reproducible," and "in no instance did multiple determinations of the end-point upon the same specimen vary more than one tube."

The results of the six groups of investigators clearly show no consistent correlation, so that the conclusion is inevitable that the test as such is valueless. The figures obtained by Cliffton (1949), Homburger *et al.* (1950), and ourselves, all using the original technique, are directly comparable, and contrast sharply with the results quoted by Huggins *et al.* (Table I).

We had hoped that the test might have some application in the diagnosis of malignant disease in the chest or abdomen. In our experience, however, strongly positive tests were nearly always obtained in acute and chronic inflammatory lesions of the chest and in haemorrhagic states in the alimentary tract not associated with malignancy (Table II).

The conclusion, therefore, is that the change in serum proteins manifest as altered thermal coagulability is not invariably present with malignant disease, even in clinically advanced lesions, and also occurs in a high proportion of cases with non-malignant pathology and even in apparently healthy individuals. The cause of such a change is not necessarily related to an alteration in the total serum proteins. The nature of the change is as yet obscure.

Summary

The thermal coagulability of serum proteins in the presence of iodoacetic acid has been examined in 65 normal individuals, 89 cases of malignant disease, and 63 patients with other diseases.

An "iodoacetate index" has been calculated for each serum; this has been used to assess changes in the coagulability of serum proteins in relation to disease. The distribution pattern of the figures so obtained leads to the conclusion that the determination of such an index is useless in the diagnosis of malignant disease. Not only may serum from apparently healthy individuals furnish iodoacetate figures falling into the index range suggested for cancer cases, and vice versa, but most cases of non-malignant disease gave values in the "cancer range."

The test also reveals no consistent correlation between "iodoacetate index" and the severity of the malignant condition; even advanced cases of cancer may give figures in the "normal range."

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KELL-CELLANO BLOOD GROUP SYSTEM IN PREGNANCY AND TRANSFUSION

BY

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Coombs, Mourant, and Race (1946) described a new antigen-antibody system (Kell) unrelated to the Rh system but nevertheless capable of producing haemolytic disease of the newborn. More recently, Levine *et al.* (1949) found another antibody (Cellano) which also caused haemolytic disease of the newborn, and showed that the Kell and Cellano genes are alleles. They suggested that the symbols K and k, previously employed to represent Kell-positive and Kell-negative, be used to indicate the presence of the Kell and Cellano genes respectively, and calculated that the three genotypes, KK, Kk, and kk occur with frequencies of 0.2%, 8.6%, and 91.2% respectively among white Americans.

Six examples of anti-Kell are noted in their paper and at least a dozen others are known at the present time (R. R. Race—personal communication). The Kell antibody in the case described here was discovered at the Sheffield Blood Transfusion Centre in 1948 (Dunsford, 1949), and is exceptional in reacting in saline but not in human serum or bovine albumin.

Case History

The patient, aged 38, was first seen on March 12, 1948, when she was admitted to hospital at the 33rd week of gestation in her third pregnancy, on account of intrauterine foetal death. Her previous obstetrical history, which was somewhat chequered, was as follows.

1. On March 1, 1929, she gave birth in her own home to a living female mature infant weighing 9½ lb. (4.3 kg.). Postpartum haemorrhage occurred and she was removed to a non-obstetrical general hospital, where two blood transfusions were given on the day of admission, each transfusion apparently of one pint (570 ml.) and each from a separate donor. Septicaemia supervened, but full recovery occurred after four weeks, when she was discharged. Unfortunately the transfusion records could not be found and so the donors could not be traced.

2. A stillborn male mature infant was born at home on January 21, 1932; weight unknown. Foetal movements were not felt by the patient for six weeks before delivery. No investigations were made. She divorced her husband in 1936, but remarried in June, 1947. The first husband, unfortunately, cannot be traced, and so no investigations on his blood are possible.

3. On March 16, 1948, a stillborn macerated male foetus was delivered; gestation 34 weeks. She had booked for home

confinement with her third pregnancy (the first by her second husband), and delivery was due in the last week of April, 1948. At the third month she had a threatened abortion, treated by her own doctor with rest in bed at home, and from then onwards until March 1, when she failed to feel the foetal movements, there were no further complications. Her past history yielded no illnesses of note. Examination on March 12 showed her to be a normal healthy woman, no abnormality in blood pressure or urine being present. The Wassermann reaction and Kahn test were negative. The fundus was small for 33 weeks' gestation, and the foetal heart sounds were absent. A skiagram of the foetus showed a well-marked Spalding sign, and so induction of labour by the insertion of a stomach tube into the lower pole of the uterus was performed on March 16, and 21 hours later a male stillborn macerated foetus weighing 3 lb. 8 oz. (1.6 kg.) was delivered without event. Her recovery was spontaneous and she was discharged on March 26. At the post-natal examination on April 27, when recovery was complete, she was advised to report immediately to the hospital antenatal clinic if any further pregnancy occurred.

4. On November 13, 1949, she gave birth to a living male mature infant. She reported on June 1, 1949, when she stated that her last menstrual period had begun on February 1 and she thought she was pregnant. Examination showed her to be 16 weeks advanced in pregnancy and her general condition to be wholly normal. Her antenatal progress to term was smooth and no obstetric complications occurred. On November 13, as she had not gone into labour spontaneously and had exceeded the calculated date of delivery by some five days, a surgical induction of labour (low rupture of membranes) was performed, and six hours later she delivered herself spontaneously of a living male mature infant, weighing 6¼ lb. (2.8 kg.). The placenta and membranes showed no abnormality, either macroscopically or microscopically, and the infant was at no time jaundiced or anaemic. Both mother and infant made normal progress and were discharged 10 days afterwards. At the post-natal visit one month later the infant was making excellent progress and the mother was overjoyed at the successful outcome of her pregnancy.

Serological Investigations

The patient's blood was first tested in October, 1947, when she was 14 weeks pregnant: no abnormal antibodies were found, but the laboratory recorded "? weak reactions with two cells (C_1 and C_2)." C_2 was known to be Kell-positive, but the Kell type of C_1 was unknown, and no particular significance was attached at the time to these doubtful reactions. (C_1 subsequently proved to be Kell-positive also.)

Blood collected from the mother at the delivery of a stillborn child in March, 1948, was found to contain anti-Kell active at 37° C. in saline and demonstrable with anti-human globulin, but inactive in human serum or bovine albumin. This is of interest, as it was the first saline agglutinating Kell antibody reported, and Sanger *et al.* (1949) had noted that all three examples of the Kell antibody reported up till then had been of the incomplete type, and that this fact was probably not without clinical significance.

The patient became pregnant again in February, 1949, and was delivered of a normal full-term child in November, 1949. Her blood was examined three times during this pregnancy—at the 20th, 28th, and 35th weeks—as well as at delivery and on the 14th day post partum, and on each occasion saline agglutinating anti-Kell could be demonstrated. The titres in saline on these occasions were 1, 4, 1, 2, and 2 respectively, and the corresponding titres with anti-human globulin were 2, 64, 32, 8, and 32. On no occasion did her serum agglutinate Kell-positive cells suspended in human serum or bovine albumin, and the Coombs test after inactivation of her serum at 70° C. for 10 minutes was consistently negative.

The patient was Group O Rh-positive (CDe/cDE), M, P, Le^a-negative, Kell-negative, Cellano-positive (presumably kk).

Her second husband was Group B Rh-positive (CDe/CDe), MN, p, Le^a-positive, Kell-positive, Cellano-positive (presumably Kk).

The baby was Group O Rh-positive (CDe/CDe), MN, P, ? Le^a-positive, Kell-negative, Cellano-positive (presumably kk). The direct Coombs test was negative.

Discussion

In the absence of records of the bottles of blood transfused in 1929 and because of our inability to trace her first husband, it is not possible to say with certainty whether the patient had been immunized against the Kell factor by blood transfusion, pregnancy by the first husband, or pregnancy by the second husband, who is known to be Kell-positive. However, in view of the fact that the second child of her first husband was stillborn but mature, and her third child, the first child of her second husband, was stillborn, macerated, and only 34 weeks in gestation, the probabilities are that she was immunized before her second marriage and by the blood transfusion in 1929 rather than by her first or second child. It would be a remarkable coincidence if her first husband and her second were Kell-positive, the odds being about 130 to 1 against such an event occurring.

This investigation supports Levine's view that the genes for the Kell and Cellano factors are allelomorphic, in that the husband was Kk, the wife kk, and the child kk. It also draws attention to the fact that an increasing titre of an antibody during pregnancy does not necessarily indicate that the foetus carries the corresponding specific antigen. In this case the foetus was Kell-negative, yet the titre of the maternal anti-Kell increased during pregnancy. This phenomenon has been observed on many occasions in the case of Rh antibodies, and is believed to be of the nature of an anamnestic reaction, the foetus providing a non-specific stimulus.

This Kell antibody is peculiar in reacting in saline and with anti-human globulin but not in human serum or bovine albumin. Indeed, albumin seems to suppress its activity instead of enhancing it.

During these investigations, with the use of the patient's antibody, the cells of two unrelated persons were observed to give much weaker reactions than the other Kell-positives, and another cell was not agglutinated in saline suspension but was sensitized, as evidenced by a positive reaction with anti-human-globulin serum. This suggests that variants of the gene K exist, some of which may behave in a manner similar to D^u cells in the Rhesus complex.

The patient generously donated blood containing this valuable antibody, which has been used, together with anti-Cellano serum kindly supplied by Dr. Philip Levine, for determining which Kell-positives are homozygous. Systematic search is now being made for the Kell antibody in pregnancy and in cases in which a transfusion reaction has occurred. The results of these investigations will be published in another paper, but they already demonstrate (in confirmation of the work of other investigators) two points of practical significance: (1) the Kell antibody is of considerable clinical importance as a cause of transfusion reactions and of haemolytic disease of the newborn; and (2) its presence can be demonstrated by means of the indirect Coombs test but will not usually be detected by routine cross-matching techniques ordinarily employed in hospitals.

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Medical Memorandum

Vaginal Hysterectomy for Complete Rupture of Uterus during Labour

The following case is recorded, in spite of the fatal termination, because the operative procedure described might be of value to other obstetricians confronted with the same complication under similar working conditions.

Case Report

A Yoruba multipara aged 23, who had not attended the antenatal clinic, was admitted at term on April 6, 1950, having been in labour for nine hours, the membranes having ruptured at the beginning of the uterine contractions. Before admission she had been bearing down in the customary kneeling position for some three hours without advance, and this was followed by absence of uterine contractions for the next three hours. She had had no sudden abdominal pain, fainting, or shoulder pain, and no bleeding per vaginam.

On examination her temperature was 99° F. (37.2° C.), pulse 120, respirations 28, and blood pressure 80/40 mm. Hg. There was some degree of anaemia, and she seemed restless, with mild continuous lower abdominal discomfort. The abdomen was tense, and markedly tender below the umbilicus, up to which the bladder extended. Foetal parts were difficult to define except in the epigastrium, where the breech was located. The foetal heart was not heard.

Rectal examination revealed that the cervix was fully dilated, and a marked caput could be felt in low mid-cavity. Under thiopentone and open ether anaesthesia, and after catheterization, vaginal examination revealed that the head was arrested deeply in the left transverse (L.O.T.) position, with a marked caput. The sacral promontory was acutely projecting forwards, the diagonal conjugate was 4½ in. (11.4 cm.), the upper half of the sacral bay was straight, and the pelvic outlet was normal. On withdrawing the hand there was a free loss of blood. On re-examination a complete rupture of the uterus was found at the utero-vaginal (syn. cervico-vaginal) junction, extending along the whole of the anterior surface from half-way along the left lateral margin to the right antero-lateral margin of that junction. The foetal body and limbs and the placenta and membranes had been extruded into the peritoneal cavity, and the uterus, which was lying in the right iliac fossa, was freely mobile.

In view of the presence of active bleeding, which might have been arising from the left uterine artery, it was considered wiser to act at once, because there was no possibility that the operating theatre would be available for at least two hours, and blood donors and a qualified anaesthetist were not available. Moreover, the patient's general condition was now poor —pulse 140, blood pressure 80/30 mm. Hg.

After an unsuccessful attempt at manual rotation it was considered unwise to rotate and deliver with Kielland's forceps, which might have extended the tearing. The head was pushed up, and an intraperitoneal podalic version was easily performed, followed by a breech extraction of a fresh stillbirth, weight 6 lb. 3 oz. (2.8 kg.). The placenta and membranes, weighing 19½ oz. (0.55 kg.), were manually removed from the peritoneal cavity through the uterine rent. It is the routine here at operations to have four sponge-holders placed on the instrument trolley for post-partum inspection of the cervix. While the uterus was being pushed into the pelvis to reveal and facilitate clamping the free margins of the tear, it was found that the uterus was so mobile that it descended to the vaginal outlet. A vaginal hysterectomy was then regarded as possible, whereupon two fingers were hooked into the uterine cavity and with further suprapubic pressure the fundus of the uterus was delivered under the symphysis pubis. The Fallopian tubes, ovarian vessels, round ligaments, and broad ligaments were clamped and divided in the usual fashion, and ligated with No. 2 catgut, followed by reconstitution of the vaginal vault. In view of the difficulty of ligating the lower end of the tear on the left in the region of the utero-vaginal junction, two clamps were left *in situ*. Haemostasis being ensured, the vagina was then packed with gauze soaked in 1 in 1,000 acriflavine, and an indwelling catheter inserted into the bladder.

Immediately after the operation the pulse was imperceptible and the blood pressure was 40/0 mm. Hg. Some 30 minutes after an injection of ¼ gr. (50 mg.) of ephedrine intramuscularly, 1.7 ml. of nikethamide, and 8 min. (0.48 ml.) of adrenaline hydrochloride (1 in 1,000) the blood pressure was 80/40 and the pulse 150. The patient continued to make excellent progress, and was given antibiotics, antitetanus serum, and the antimalarial quinine sulphate.

Fifteen hours later, when the temperature was 99.6° F. (37.55° C.), pulse 112, and blood pressure 112/58 mm. Hg, the packing, clamps, and catheter were removed, after which there was no bleeding. Early removal of the packing and clamps is considered to be essential in tropical climates because of the danger of sepsis. Progress continued to be good, with minimal distension and no vomiting, until on the third day, 68 hours after operation, she suddenly collapsed and died within 30 minutes.

Post-mortem examination revealed a large quantity of free blood in the peritoneal cavity, with some localized plastic peritonitis around the left ovario-pelvic ligament, from which the secondary haemorrhage appeared to have arisen. There were no other abnormalities and no bleeding per vaginam. It was of interest to note the firmness and effectiveness, against subsequent prolapse of the bowel, of the reconstituted vaginal vault, which was sloping downwards and backwards from behind the bladder and symphysis pubis towards the hollow of the sacrum.

Comment

There is no doubt that laparotomy performed some two hours later would have been fatal, should the patient have survived that interval of time until the operating theatre had been vacated. Alternative procedures would have been to displace the head or to perforate and extract and to attempt to secure the free margins of the uterine rent with clamps, and then to perform a laparotomy at the first available opportunity. This would have necessitated a second anaesthetic, haemostasis might not have been successfully secured by the clamps, and blood donors would still not have been available.

Until the patient's sudden death the post-operative condition (after the first half-hour) was good. This fact is worthy of note, because the convalescence has been stormy in our cases of ruptured uterus that have survived laparotomy.

The operation was simple and rapid, under conditions in which irritating delays can lead to a fatal issue. The uterus, which weighed 26½ oz. (0.75 kg.) and was 6½ in. (16.5 cm.) in length, 5 in. (12.7 cm.) broad, and 3 in. (7.6 cm.) in thickness, was easily made to traverse the pelvic cavity.

In future, silk sutures rather than catgut, as used in this case, would be preferable for ligating the enlarged vessels associated with pregnancy, and also because of the added danger of infection in the Tropics. Perforation and extraction might be preferred to the procedure of extraction adopted, with less risk of infection and trauma.

The operation of vaginal hysterectomy is therefore advocated for the type of rupture here described, which was an extensive one at the utero-vaginal junction, producing unusual mobility of the uterus; and particularly is it recommended in this form of rupture when the facilities for immediate laparotomy and resuscitation are not available.

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Reviews

EYE SURGERY

Ophthalmic Operations. By Seymour Philps, F.R.C.S. (Pp. 397; 510 figures. £2 10s.) London: Baillière, Tindall and Cox. 1950.

Eye Surgery. By H. B. Stallard, M.B.E., M.D., F.R.C.S. Second edition. (Pp. 683; 550 illustrations. £2 12s. 6d.) Bristol: John Wright and Sons. 1950.

Since the war, perhaps because of it, ophthalmology has been enriched with a number of excellent textbooks on ophthalmic surgery. They have appeared from America, France, Spain, and Italy, and Great Britain has its own notable contributions to add. Philps's *Ophthalmic Operations* is the linear descendant of that well-known companion of a previous generation by Grimsdale and Brewerton (2nd ed., 1920) and is a product of the same hospital; it is a striking tribute to the revolutionary progress that ophthalmic surgery has made. Within its limitations Philps's book is thoroughly good. It is a record of the techniques employed personally by an outstanding surgeon of considerable experience, without discussion or description of alternative methods and without bibliographical references. It therefore cannot serve as a reference book; but there is much to be said for this method of presentation, particularly as a practical guide for surgeons starting ophthalmic work.

The volume covers ophthalmic surgery systematically. Chapters on general considerations and anaesthesia are followed by a systematic description covering the whole field of operations on the eye and its adnexa. The author discusses each procedure under the headings of indications, anaesthesia, instruments required, technique, and (where applicable) special nursing and complications. Each section is clearly illustrated, mainly by unusually satisfactory photographs (all the author's own) supplemented by diagrams (all drawn by the author); these are a feature of the book, and it would seem that the hands of the ophthalmic surgeon are allied to those of an artist. The writing is clear, the teaching sound (perhaps a little dogmatic on occasions), and the technical production of the book unusually good. It is a creditable addition to the literature and will make and maintain an assured place for itself.

It is good to see Stallard's *Eye Surgery*, originally published in 1946, reach its second edition. The book is so well known among ophthalmic surgeons that a detailed account of its manner of treating the subjects is unnecessary. The new edition, however, has been very much enlarged—by almost 200 pages—increasing its bulk by one-third, and by 212 new illustrations. These are useful, and the author's apology in his preface that they are practically all his own work is quite misplaced modesty. The added material includes all the important innovations introduced into the practice of surgery during the last five years, while the author pays particular attention to such subjects as corneal grafting and keratectomy; recent operations for glaucoma such as goniotomy, cyclodiathermy, and the insertion of drains into the anterior chamber; scleral resection for retinal detachment; and the new techniques for the insertion of implants after enucleation. Each procedure is discussed with the meticulous detail characteristic of all the author's work. As in the previous edition, the section on the lids and their plastic reconstruction is unusually elaborate; indeed, it receives more space than is allotted to the surgery of the lens, choroid, retina, and glaucoma together. The whole book is enriched with personal case reports and good photographic records drawn from the author's practice. There is no doubt that this second edition will perpetuate and enhance the reputation of its predecessor.

STEWART DUKE-ELDER.

MODERN KNOWLEDGE OF MENSTRUATION

Menstruation and its Disorders. Proceedings of the Conference held under the auspices of the National Committee on Maternal Health. Edited by Earl T. Engle. (Pp. 358; illustrated, 37s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

This book records the proceedings of a conference on menstruation organized by the National Committee on Maternal Health in the U.S.A. and, like so many works of this kind which have appeared in recent years, makes fascinating reading. The title is in some ways misleading, for there is no attempt at a complete account of menstruation, the 13 contributions dealing only with the "growing points of knowledge" and serving to indicate modern trends in thought and research. Each aspect is presented by one or more experts in a particular field to an audience of experts, and the reports of the discussions add to the value of the work.

Here will be found in a concise and easily understandable form the latest intricate work on the histochemistry and histophysiology of the cervix, endometrium, and ovary; on uterine and peripheral vascular changes in relation to menstruation; on endometrial pathology in some forms of functional uterine haemorrhage; on menstrual toxin; on early fertilized human ova; and on some aspects of myometrial activity. The list of contributors is in itself sufficient to attract many readers, and includes such names as Wislocki, Gomori, Hertig, Okkels, Markee, Olive and George Van S. Smith, Shorr, TeLinde, and Woodbury, with Engle editing the volume. The general standard of the chapters does not fall below the high level which is to be expected from workers of such eminence; indeed, each deserves separate review. All those who wish to keep abreast of modern developments in the study of uterine function, and those who aim at research in this field, cannot fail to find in this book both information and inspiration.

T. N. A. JEFFCOATE.

THE TIME OF OVULATION

Die Physiologie der Zeugung des Menschen. By Dr. Hermann Knaus. 3rd revised edition. (Pp. 485; 104 illustrations, 43 tables. M. 50.) Vienna: Wilhelm Maudrich. 1950.

Mosaic law enjoins the faithful to restrict sexual intercourse to the second week after menstruation, the period during which we now know ovulation is most likely to occur. Thus does modern research substantiate ancient precept. The credit for this comparatively recent discovery must go almost exclusively to Ogino and Knaus, and the latter, in this book on the physiology of human reproduction, has now collected in one volume the results of nearly twenty years' work in this field. The book makes fascinating reading, for, though much of its content is familiar through the author's many previous publications, the co-ordination has been carried through with characteristic German thoroughness, so that one has for the first time a complete survey of a complex and intricate subject.

The book is mainly about the establishment of the exact time of ovulation, and the various methods used in its determination—animal experiment, hormonal estimation, endometrial and vaginal biopsy, temperature-shift recording, and biological research—are exhaustively described

and individually discussed. It is, in fact, a scientific apologia for the author's main thesis—the "safe period." Though many a disgruntled parent may be doubtful of the veracity of the adjective, Knaus's pioneer work remains of paramount scientific interest.

ALBERT DAVIS.

HEALTH SERVICES

The Health of the People. By S. Leff, M.D., D.P.H. (Pp. 288. 12s. 6d.) London: Victor Gollancz. 1950.

In the first half of this book the author gives a historical survey of the condition and needs of the people from mediaeval times to the present day and of the medical services provided to meet those needs. There is ample room in literature for such a survey, and Dr. Leff provides a thoughtful and excellent summary of the birth and growth of the health services. The book is well written and well documented. His account includes maternity and child welfare, poor-law, municipal, and voluntary hospitals, and dispensaries and contract practice. The social and political background of the people, an essential to any health survey, is fully considered. The general reader, medical and lay, will find this part of the book of absorbing interest, and it should not be missed in particular by those whose duty it is to teach medical students, health visitors, and sanitary inspectors.

The second part of the book adds to the growing list of publications on the national health services. Here again is a careful and informative review of these services, together with a sound running commentary about them. I should have welcomed more information and more consideration in relation to general practice than is given in a short chapter, for, as the author himself says, "The general practitioner is in the front line in the battle against disease."

Those who are concerned with the industrial medical services will be much interested in the chapter on this subject—a difficult one which is becoming more and more controversial. Most medical practitioners will welcome Dr. Leff's suggestion that the problem could be solved by employing general practitioners in a part-time capacity in the factories: he properly rejects the idea of an increase in the whole-time industrial medical staff.

This book is easy to handle and easy to read. It should find a place on the book-shelves of all interested in the present health services and their development. Its undoubted value would be enhanced by the provision of an index, a criticism which could be met in the next edition, which will no doubt be required at no distant date.

C. METCALFE BROWN.

TEXTBOOK OF PAEDIATRICS

Lehrbuch der Kinderheilkunde. By R. Degkwitz, E. Glanzmann, Fr. Goebel, J. Jochims, K. Klinke, Ff. Klose, E. Rominger, and B. de Rudder. Edited by E. Rominger. Fourth and fifth editions. (Pp. 971; illustrated. M. 49.80.) Berlin, Göttingen, Heidelberg: Springer-Verlag. 1950.

Professor E. Rominger, of Kiel, has edited what is curiously described as the fourth and fifth editions of the *Lehrbuch der Kinderheilkunde*, there being no clue to this nomenclature, and mention of a second edition in 1942 in the preface makes it even more difficult to understand. Whatever the explanation, this volume can be welcomed as an exposition of the German school of paediatrics, well produced, with excellent illustrations in the text, including some in colour, of which those depicting varieties of stools are of doubtful practical use. Early sections on growth and development, on constitutional factors and hereditary disease, are rather heavy going. But with the succeeding chapters, in which clinical aspects of, for example, the infectious fevers and tuberculosis are discussed, the traditional careful attention to detail and the well-written descriptions of bedside observations show that there are available to-day worthy successors of the giants of the past. It is sad that one of the eight contributors, Professor Goebel, of Düsseldorf, has recently died and that Professor Degkwitz has moved to the United States.

There are inevitable gaps in the book and uneven patches, due, without doubt, in part to Germany's being cut off for several years before, during, and after the war from the easy intercourse of international gatherings and the free flow of scientific literature. The sections on the newborn are rather disappointing, and the account of rhesus incompatibility in the section on diseases of the blood is too brief. A list, running to over 30 pages, of medicaments used in childhood is dominated by proprietary names, which lessens its usefulness outside Germany. But these are not major blemishes, and it is good to see that paediatrics in Germany is recovering its place.

ALAN MONCRIEFF.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Recent Advances in Physical Medicine. Edited by F. Bach, M.A., D.M., D.Phys.Med. (Pp. 490. 27s. 6d.) London: J. and A. Churchill. 1950.

Acute Head Injury. By J. P. Evans, M.D., Ph.D. (Pp. 115. 16s. 6d.) Oxford: Blackwell Scientific Publications. 1950.

The Esophagus and Pharynx in Action. By W. Lerche, M.D. (Pp. 222. 40s.) Oxford: Blackwell Scientific Publications. 1950.

Selected Papers from the Royal Cancer Hospital (Free) and the Chester Beatty Research Institute. Vol. 5. (Pp. 483. 16s.) London: Royal Cancer Hospital. 1950

Cleft Palate and Speech. By M. E. Morley, B.Sc., F.C.S.T. 2nd ed. (Pp. 160. 12s. 6d.) Edinburgh: E. and S. Livingstone. 1950.

Juniors. By G. H. Pumphrey. (Pp. 162. 8s. 6d.) Edinburgh: E. and S. Livingstone. 1950.

The Rationalist Annual, 1951. Edited by F. Watts. (Pp. 88. 2s. 6d. paper covers, 4s. 6d. cloth covers.) London: Watts. 1950.

The Sex Hormones. Ciba Handbook No. 4. (Pp. 186. Free of charge.) Horsham: Ciba Laboratories Limited. 1950.

John Hunter. By S. Roodhouse Gloyne, M.D (Pp. 104. 15s.) Edinburgh: E. and S. Livingstone. 1950.

Amputation Prosthetic Service. By E. H. Daniel. (Pp. 327. 54s.) London: Baillière, Tindall and Cox. 1950.

A History of English Public Health, 1834-1939. By W. M. Frazer, O.B.E., M.D., M.Sc., D.P.H. (Pp. 498. 35s.) London: Baillière, Tindall and Cox. 1950.

Textbook of Physiology and Biochemistry. By G. H. Bell, B.Sc., M.D., F.R.F.P.S.G., F.R.S.Ed., and others. (Pp. 918. 45s.) Edinburgh: E. and S. Livingstone. 1950.

British Encyclopaedia of Medical Practice. Edited by Lord Horder, G.C.V.O., M.D., F.R.C.P. Vol. 3. 2nd ed. (Pp. 669. 60s. per volume.) London: Butterworth. 1950.

Pediatric X-Ray Diagnosis. By J. Caffey, A.B., M.D. 2nd ed. (Pp. 862. $22.50 or 169s.) Chicago: The Year Book Publishers; London: H. K. Lewis. 1950.

Semaine d'Etude sur le Problème Biologique du Cancer. A symposium. (Pp. 348. No price.) Rome: Pontifical Academy of Sciences. 1950.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY NOVEMBER 25 1950

INQUIRY BY QUESTIONARY

It is the results rather than the methods of Professor Bradford Hill's inquiries into the doctor's work and pay that have commanded the interest of the medical profession. But in giving his inaugural address[1] (briefly reported at page 1218) on November 22 as president of the Royal Statistical Society he dwelt rather on the techniques he had used, for he had had to elicit facts by questionary from people whom he had not met, whose accuracy might be questioned by the Government, and whose reticence or eagerness to co-operate might have resulted in the subjects rather than the investigator deciding what was or was not relevant. That both Spens Committees and the Government accepted Professor Hill's tables as an accurate plan by which to dispose many millions of pounds of public money is a tribute to his methods. The fact that negotiations are still proceeding with those original maps on the table is not from any doubt of their accuracy but due rather to argument about how far they refer to the changed country we know to-day. Professor Hill was addressing an audience of statisticians, but concluded his address in the hope that his inquiries would "offer something of *general* interest, and especially in the statistical field of survey work—indeed in its most dangerous and treacherous form, the inquiry by *questionnaire*." Interest in the methods should in fact be more general than he suggested. Many doctors doing clinical research but not claiming to be statisticians carry out investigations that require a sceptical care in appraising the evidence: no technical skill can bring sharp definition to a photograph that was taken out of focus, though some handsome retouching is occasionally attempted both in photography and in research. Commonly enough a doctor treats a series of cases and then follows them up, perhaps a year later, by means of a postal questionary. He is lucky if all his patients can be traced, or if traced reply, or if replying write objectively; luckier still if they can be found and will reply five years later. Some of the methods Hill used are applicable in such an investigation and are worth studying in detail when his address is printed in full.

[1] To be published in the *Journal of the Royal Statistical Society*.

In the first inquiry he was asked by the B.M.A. to find out how many services of various kinds insurance practitioners gave to their N.H.I. patients. They included attendances, visits, operations, injections, certificates, and reports. Because of seasonal fluctuations in illness the inquiry had to cover a year. The "universe" of N.H.I. practitioners was known; a randomly selected sample was chosen so large (over one-third of the total body) that the doctors taking part did not need to keep records for the whole year or of all the services on which information was sought. Sub-samples were then allotted to each month of the year, and the doctors in each sub-sample kept records for one month only. Having thus reduced the task for each doctor to one month's duration, Hill then lightened the burden further by splitting the sub-samples into groups, and asking doctors in each group to supply special information on those topics that were of subsidiary interest. All the doctors in each sub-sample therefore kept records of attendances and visits, while doctors in each group within the sub-sample kept records special to that group —of operations, or injections, or certificates, and so on. Thus the number of doctors who neglected to make a return was very small, as Hill pointed out, "by virtue of the experimental design." Given the opportunity of designing a questionary the investigator is apt to forget that data are easier to assimilate than to produce. He may avoid frightening his subjects into silence by spreading the work among them in some such way as this. The results were carefully checked for consistency by the usual methods, and their uniformity suggested that the samples were good and the records efficiently kept.

Professor Bradford Hill's second inquiry was into the professional income and expenditure of general practitioners in 1936–8. It was carried out in 1945 for the B.M.A. so that accurate evidence could be presented to the Spens Committee on remuneration of general practitioners. Here again there was a ready-made "universe," obtainable through the Central Medical War Committee; but it had a serious defect, for the sample drawn from it could contain, of the doctors practising in 1938, only those still alive in 1945. The incomes of doctors who had died between those years could not be included; their omission affected the figures for the older doctors, and gave incorrect weightings to the older age groups if all ages were combined. The response was disappointing and only two-thirds of the required sample was obtained. Failure by doctors to answer requests to take part in the inquiry was not related to age, but refusal to co-operate was, being more prevalent among the older. Though the circumstances of this inquiry militated against a wholly successful result, for the information required was nearly 10 years old and at least 1,000 of the doctors approached were in the

armed Forces, the Spens Committee accepted the figures as sufficiently accurate. No doubt it did so mainly because every care had been taken to choose the sample by random methods. Though they could not be wholly successful, any departure from them would have vitiated the results. No juggling with a sample will make it random once it has been drawn, but probable departures can be discovered, as they were here, and some allowance made for them.

After the general practitioners came the consultants with their Spens Committee. An initial problem was that no defined "universe" existed from which a sample could be drawn. With the help of the Central Bureau of Hospital Information and medical officers of health, Hill succeeded in identifying about 6,000 possible subjects for the inquiry. Replies were received from 4,793 doctors, but about half of these were not relevant to the inquiry because they were not engaged predominantly in consultant or specialist practice in 1938–9. In the general-practitioner inquiry it was thought that some doctors had refused to co-operate because they were asked to sign their returns. This objection was now overcome by asking the consultant to give the required information, unsigned, on one form, and to state on another form, over his signature, that he had filled in the first. The two forms were sent to separate addresses and thus could not be linked.

Requiring a small sample, which could be followed up if necessary, to use as a check against the large mass of returns, Hill had to adopt a special, and indeed ingenious, device to enable him to separate the forms in this sample from the bulk of them when they were returned to him unsigned. At the bottom of 90% of the forms the instruction "[P.T.O." was set; in 10% of them, which were to constitute the special sample, the bracket was omitted. The names in the sample, as in the main group, were known to the secretaries of the committee collecting evidence, but they saw no income returns; only these, and whether or not they were in the special sample, were known to Professor Hill. If a doctor in the sample did not respond, that would be known to the committee, and he could be asked again; Hill knew only how many of the sample doctors had failed to reply, not which ones. By using both halves of the information secrecy was maintained and defections were followed up. Cross-checks between sample and main group on such features of the investigation as failure to reply, distribution of specialists by specialty, and mean net income indicated that the special sample had been a useful device and that the figures of the main inquiry could be accepted "without serious qualms."

Such in brief were some of the methods used. They depend for their efficacy not on abstruse mathematical procedures but on the realization that a sample from which generalizations are made must be unbiased. Neither the investigator nor the subjects he is investigating must allow their preconceptions, albeit unconscious, to influence the composition of the sample. Such perfection is rarely possible in inquiry by questionary; checks must therefore be introduced to test departure from it. The methods require clear thought, not elaborate technique, and they are such as any medical man can apply when carrying out an investigation, however slight.

TERRAMYCIN

If "aureomycin" and "chloromycetin" (chloramphenicol) may be described as the newer antibiotics, then the newest is "terramycin," at least among those with any assured therapeutic future. The clue to American success in producing this series of valuable antibiotics is to be found in their names. Each of these from streptomycin onwards is derived from a soil actinomycete, and several American firms have for some time been engaged in examining samples of soil from all parts of the world in the hope of discovering new organisms of this type forming hitherto unknown antibiotics. Laboratories so engaged have examined many thousands of such samples and screened immense numbers of cultures from them. The more promising are submitted to closer investigation, including, in particular, tests of toxicity of the antibiotics formed by them. It has been said that several hundred thousand cultures may be examined in order to find one or two worthy of going forward to the pilot-plant stage—that is, production on a scale adequate for thorough experimental and possibly clinical trial. Such work involves a large and continuous outlay, which may or may not reap a gigantic reward. To those manufacturers whose efforts have been fortunate must now be added the name of Pfizer and Co.—familiar to many as the makers of much of the penicillin used in the Army and elsewhere during the latter part of the war—for terramycin is their product. Its existence was announced in the early part of this year,[1] and since then it has undergone extensive therapeutic trial. The main source of information on this product is the report[2] of a conference devoted to it which was held by the Section of Biology of the New York Academy of Sciences in June last. The authors of the 32 papers include many of those who have done pioneer work in the clinical study of other antibiotics from penicillin onwards, and their combined contributions give a good general picture of what terramycin may be expected to do.

[1] See annotation in the *British Medical Journal*, 1950, 1, 1309.
[2] *Ann. N.Y. Acad. Sci.*, 1950, **53**, 221–460.
[3] Ibid., p. 253.
[4] Ibid., p. 309.
[5] Ibid., p. 266.
[6] Ibid., p. 297.
[7] Ibid., p. 448.

In this country the first report on terramycin comes from Drs. W. D. Linsell and A. P. Fletcher, whose paper appears in this issue at page 1190. Besides describing the pharmacological properties and range of antibacterial activity of this antibiotic, they also record its clinical effects in a preliminary series of 29 cases. Terramycin is an amphoteric substance, solutions of the sodium salt having an alkaline and of the hydrochloride a strongly acid reaction. It differs from aureomycin, which otherwise it closely resembles, in that solutions of its hydrochloride are comparatively stable. Both salts and the parent compound itself have been shown to be active against experimental infections. For the treatment of human disease the hydrochloride has generally been used and has been given in capsules by mouth in doses totalling usually 4 g. daily. Although the drug remains detectable in the blood for as long as 24 hours after a single dose its concentration begins to fall off after about six hours, and this interval between doses has therefore been generally adopted. Larger doses do not give correspondingly higher blood levels, there being apparently a limit to the amount which can be absorbed. Whatever the dosage, much of the drug remains in the bowel, attaining high concentrations in the faeces and suppressing most of the normal flora: here again its behaviour is like that of aureomycin. A point of difference from aureomycin is its minimal penetration into the cerebrospinal fluid, but it reaches serous effusions and the foetal circulation and has been found in high concentrations in the bile. The concentrations attained in the urine, according to Welch,[3] are higher dose for dose than those of either aureomycin or chloramphenicol, though those found in the blood are intermediate between the levels attained by these two drugs—those of chloramphenicol being the highest.

Terramycin has a broad "antibacterial spectrum," resembling that of aureomycin in the generally higher order of sensitivity among Gram-positive species. *Proteus* is highly resistant and *Ps. pyocyanea* variable in its sensitivity. That the more sensitive strains of this species can be controlled by the drug is shown in some of the cases treated by Linsell and Fletcher. *Myco. tuberculosis* has a degree of resistance which seems unpromising. Steenken and Wolinsky[4] nevertheless obtained distinct therapeutic effects in tuberculosis of both guinea-pigs and mice, hampered in the former by the exceptional toxicity of the drug to this animal. The action of terramycin is predominantly bacteriostatic, but higher concentrations acting on smaller numbers of bacteria are bactericidal.[5] Resistance, when acquired *in vitro*—it does not so far appear to have been observed in treated patients—is that of the "penicillin type," gradual in development and moderate in degree; the greatest increase obtained artificially by Gocke and his colleagues[6] was 64-fold. Herrell and his colleagues,[7] in similar studies, have made the important observation that organisms made resistant to terramycin also regularly become resistant to both aureomycin and chloramphenicol but not to streptomycin; indeed, sensitivity to the latter may be slightly increased.

Clinical trials of terramycin have ranged over a wide variety of conditions, and their results in infections due to sensitive bacteria have generally been very similar to those given by aureomycin. With few exceptions the two drugs appear to be practically equivalent alternatives. There are favourable reports of the action of terramycin in pneumonia, septicaemia, and urinary tract infections. It is highly effective in undulant fever, and of little or no value in typhoid fever and the typhoid carrier. It has a beneficial action in amoebiasis and is recommended for peritonitis and for pertussis. The resemblance extends to the field of virus and rickettsial infections: terramycin has a marked effect in primary atypical pneumonia, but the original suggestion of a possible action on the influenza virus seems to have been based on a non-specific action exerted by high concentrations in the chick embryo, and a therapeutic effect in this disease is not to be expected. Several other viruses are known to be unaffected by the drug, but it possesses very marked antirickettsial activity, exceeding that of either aureomycin or chloramphenicol under certain experimental conditions, particularly against *R. burneti*—a fact which will render clinical trial in Q fever of particular interest. The indications for terramycin in specific diseases are thus already well defined, but, as we are reminded by the clinical part of Linsell and Fletcher's paper, there remains a great variety of wound, post-operative, and other infections in which only experience illuminated by careful bacteriological study can assess the potentialities of a new antibiotic. Presumably supplies of terramycin will be much restricted here for some time to come, but possibly further opportunities may be afforded of conducting trials in this country, if only for limited purposes.

DURHAM AND THE DOCTORS

The action of the Durham County Council in making trade union membership a condition of employment has provoked prompt reaction on the part of the teaching and medical professions. On November 10 the county M.O.H., on the instructions of the Durham County Council, asked all medical officers employed by it to supply him on or before November 22 with evidence of membership of "an appropriate trade union." He informed them that for doctors membership of the British Medical Association would meet the requirement. Anyone failing to produce such evidence by November 22 would cease to be employed by the

county council. Those not members of a union (or in the case of doctors of the B.M.A.) would be offered re-employment on condition they did become members of an appropriate union or of the B.M.A. As soon as information was heard of this piece of bureaucratic blundering, the Secretary of the B.M.A., Dr. Angus Macrae, asked the Durham county medical officer of health for full information. After receiving a letter from the clerk to the county council, Dr. Macrae informed him of the policy of the B.M.A., protested strongly against the action taken, and demanded that the county council should receive a deputation from the Association. Each one of the medical officers employed by the Durham County Council was written to and urged not to comply with the county council's request and offered full support if he or she followed the Association's advice. The number of medical men and women involved is fifty-three. The British Medical Guild, from its present financial resources, will undoubtedly come to the help of any one of the medical officers in Durham who might suffer financially as the result of acting upon the principle laid down by the British Medical Association and supported, incidentally, by no less a person than the Minister of Health. This opportunity for action by the Guild should be noted by those who have hitherto had some doubt about its usefulness.

The Public Health Committee of the B.M.A. held an emergency meeting on November 16 to consider the situation and decide what action should be taken. It condemned the action of the Durham County Council and on the basis of policy laid down by the B.M.A. and the Society of Medical Officers of Health is urging the Durham medical officers not to comply with their county council's request. The chairman of the Public Health Committee, Dr. C. Metcalfe Brown, followed this up by attending personally a meeting of the officers concerned in Bishop Auckland on November 18, where both he and Dr. E. Grey Turner, assistant secretary of the B.M.A., addressed those present. An account of this meeting appears in this week's *Supplement*.

It may be recalled that the Trade Disputes and Trade Unions Act of 1946 repealed the Act of 1927, Section 6 of which made it illegal for any local or public body to require as a condition of employment that any person should, or should not, be a member of a trade union. The first repercussion of this on the medical profession was a notice of dismissal issued by the medical officer of health for Willesden in December, 1946, to those nurses and doctors in two of this authority's hospitals who did not comply with the local council's resolution that employment was conditional upon membership of a trade union. At the Willesden Municipal Hospital the sister tutor and deputy matron thus served with dismissal had been working in the hospital for 24 years, and the night sister for 26 years; but to satisfy local doctrinaire stupidity these devoted women were given a month's notice. They refused to comply with the council's requirement and it subsequently had to withdraw from an untenable position.[1] Shortly after this the Ministry of Health sent a circular to all local authorities in which the Minister reminded them that their primary duty was to maintain the efficiency and smooth running of the health service and to ensure the welfare of the patients for whom they were responsible. It was stated that the Minister was anxious that doctors and nurses should join a trade union or appropriate professional association, but considered that this matter should not be decided by unilateral action of local authorities.

The British Medical Association is resolutely opposing this fresh attempt to interfere with the private concerns of medical men, not because it fears it will lose members—membership of the B.M.A. is regarded as fulfilling the requirement demanded by the local authority—but for the simple reason that membership of the B.M.A. is voluntary and the strength of the Association depends upon this fact. Not only that, but in times when there is so much compulsion to do this or that, and to sign this document or the other, it is essential to preserve free institutions and the freedom which such institutions have to criticize without fear official bodies, whether central or local. There is another and perhaps more important point. The Medical Acts confer the right to practise medicine on men and women who, having passed certain tests, have their names placed on the *Medical Register*. To introduce another qualification such as membership of the B.M.A. or of a medical trade union is nothing less than an impertinence. As Dr. Hill observed when he raised this question in the House of Commons: "I think sometimes that we are losing our capacity for anger at such interference with the freedom of the individual." There can be no question that the majority of medical men and women in this country will do all they can to support those medical officers in Durham who have decided to refuse to comply with the demand of their county council. The many who will be indignant over what has happened may feel like following this up by making a donation to the British Medical Guild so that it will always be in a position, as it is on this occasion, to offer financial help to medical men who decide to take a stand on a matter of principle.

[1] *British Medical Journal*, 1946, **2**, 864.

INDICATIONS FOR THE NEWER ANTIBIOTICS

Major advances in antibiotic therapy have so far taken place at intervals of four years. Penicillin was first shown to be a chemotherapeutic agent and employed as such in 1940. The discovery of streptomycin, which made possible the treatment of tuberculosis, plague, and a variety

of infections due to Gram-negative bacilli, dates from 1944. The year 1948 marks the discovery of "aureomycin" and "chloromycetin," which have extended the scope of antibiotic therapy even more widely. The action of both in various forms of typhus and of the latter in typhoid must rank as their main achievements, taking precedence over all others in parts of the world where these diseases are common. To us, among whom typhoid fever is rare and rickettsial infections—but for a problematic number of cases of Q fever—are unknown, this chemotherapeutic advance has only a restricted, albeit very welcome, application. These, however, are only the outstanding uses of these two drugs: they have many others, of which we may hope to take advantage when supplies become freely available.

Three categories of use, in particular, are likely to lead to a very large demand for one or the other. It has been recognized for some years that penicillin is to some extent losing its hold on staphylococcal infections owing to the increasing prevalence of resistant strains. When penicillin fails for this purpose, aureomycin should take its place: staphylococci are uniformly susceptible to it and there is so far not much evidence of any serious tendency for them to become resistant. Staphylococcal osteomyelitis, septicaemia, pneumonia, mastitis, and severe carbuncles, if due to penicillin-resistant organisms, should therefore be treated with aureomycin. Whether less serious conditions than these should so be treated in present circumstances is doubtful. A still wider field is the treatment of urinary tract infections, for most of which aureomycin is very effective. Chloromycetin (chloramphenicol) is also effective, particularly in coliform infections, and the relative merits of these two drugs for this purpose have not yet been clearly assessed. This is another form of use in which we are not in a position to indulge indiscriminately during the present scarcity.

Perhaps the most difficult field in which to distribute exiguous supplies to the best advantage is that of lung infections. It has repeatedly been pointed out in American journals that aureomycin is the nearest possible approach to a cure-all in pneumonia: at least it has a specific effect on all recognized bacterial and virus causes of this disease. Two recent American studies supply evidence that in ordinary pneumococcal pneumonia the effect of aureomycin is at least equal to that of penicillin. Gocke, Collins, and Finland,[1] describe 33 cases—some having very unfavourable features, and 11 having bacteriaemia—in which the response to aureomycin, usually given by mouth but sometimes intravenously, was almost uniformly good and rapid. Salient features were the prompt disappearance of the organism from both blood and sputum, the equally good effect when treatment was started late, and the absence of suppurative complications. In a second paper the same authors[2] describe 13 cases of pneumonia complicating influenza, in which the sputum contained haemolytic streptococci, staphylococci, or (in one case each) *H. influenzae* or *Bact. friedländeri*. The response to aureomycin was again good. (It would be unwise to conclude from these findings that the drug has any effect on the virus of influenza itself. There is no evidence of any such action or of any effect on the common cold.) Dowling and his colleagues[3] go even further when discussing the effect of aureomycin on pneumococcal pneumonia, though their conclusions are commendably guarded. They have treated 131 cases with this drug, and from the fact that bacteriaemia was detected in 32 (24%) they may be presumed to have been of average severity. There were only two deaths, giving a mortality of 1.5%, as compared with 5.2% in a previous series of 686 cases treated with penicillin. These authors also observed that in the aureomycin-treated patients the temperature fell more rapidly. They therefore conclude that the drug is "at least as effective" as penicillin, adding, "There is a possibility that it may be even more effective."

The efficacy of aureomycin in the common forms of pneumonia is thus well established. It is also known to be effective in those due to Gram-negative organisms, in the virus infections psittacosis and primary atypical pneumonia, and in Q fever. A perfectly simple and most satisfactory policy would thus be to give aureomycin to all patients with pneumonia of whatever kind, not, indeed, troubling to find out of what kind it is when this presents any difficulty. This we cannot at present afford to do. The drug is obtainable for patients with virus pneumonia, but to decide whether application for it for this purpose is justified in any given case must often be difficult. The mere absence of pneumococci and other pathogenic bacteria from the sputum is no proof that the disease is due to a virus, particularly when chemotherapy of other kinds has already been employed, and the serological tests whereby the diagnosis can be confirmed lead to considerable delay. In isolated cases a precise aetiological diagnosis must often be retrospective, and it is only during an epidemic that the nature of the infection can be assumed with any confidence. Study of the effect of aureomycin on this group of infections should provide a clearer picture of the incidence and character of each.

[1] *Arch. intern. Med.*, 1949, **84**, 857.
[2] Ibid., 1949, **84**, 875.
[3] *J. Lab. clin. Med.*, 1950, **35**, 215.

MENTAL ILLNESS IN WEST AFRICA

The Colonial Office report entitled *Studies in Mental Illness in the Gold Coast*, by Dr. G. Tooth, directs attention to psychological stresses caused by the unequal rates of evolution of different sections of Africans under European influences. Constant exposure to tropical diseases may also predispose to mental illness: not only can organic diseases affect mental stability but a high infant mortality may be the root cause of certain social and sexual behaviours which become, during evolution, a source of mental conflict when they contravene Western conventions. The attitude towards mental illness varies in different parts of the Gold Coast: there is veneration in the northern territories, fear among the forest dwellers, and shame in the coastal areas. These differences influence the treatment of lunatics and also the form of lunacy in separate areas. Organic diseases, delusional states, schizophrenia, and affective states form the chief mental abnormalities. Less than 10% of mental patients receive asylum treatment: the remainder lodge in family compounds, board with native doctors, or roam at will, but their lot compares favourably with that of those in the asylum. Consequently, with the

Studies in Mental Illness in the Gold Coast, 1950. London: H.M.S.O.

present limited medical resources, it seems reasonable to develop this type of home or community care, possibly by the establishment of observation compounds staffed by local attendants, with farm land available for the use of the inmates. Central mental-hospital accommodation could then be reserved for rehabilitation of patients with acute and recoverable mental illness or for restraint of those with antisocial or dangerous tendencies, instead of being used as at present mainly to house chronic and irrecoverable dements. It is also suggested that in view of the complexities of the West African background the care of the insane might well remain in local lay hands until sufficient African psychiatrists are trained.

Tooth suggests that trypanosomiasis is the commonest cause of mental derangement throughout large areas of West Africa, and he appears to believe that mental symptoms are early manifestations of this infection. Although he agrees that the diagnosis of trypanosomiasis can be confirmed only by finding trypanosomes, he suggests that this procedure is often impracticable and consequently that increased knowledge of the mental changes may result in more frequent early recognition of the infection. It would have been of value if Tooth could have indicated clearly the incidence of mental changes in Africans with normal cerebrospinal fluids but with trypanosomes in the blood or gland juice, and then compared this incidence with that of mental disease in Africans in whom trypanosomiasis could not be proved. As it is, it is difficult to evaluate his conclusions on the mental changes in trypanosomiasis, especially since he adds that "it is not unlikely that similar mental changes occur in other tropical diseases." Investigations by experts of special problems among tropical populations are obviously of great value, and the Colonial Social Service Research Council is to be congratulated on initiating this inquiry. Future reports might have an even greater value if such investigations were carried out by a team of critical experts, including a specialist in tropical diseases.

JOULES AND CALORIES

In his elementary physics course the medical student learns, and later forgets, that a calorie is the amount of heat required to raise the temperature of 1 g. of water from 14.5° C. to 15.5° C. Later, in physiology, he hears of the "big calorie" of dietetics, one thousand times the unit learned in physics, and more properly called the kilocalorie (kcal.). This may satisfy physicians, dietitians, and other biologists, but has been worrying physical scientists for some time. There are in fact a number of calories in use—the 15° calorie, the International Steam Table calorie, the Mean calorie, and so on, and, since these are all different quantities of heat, confusion ensues. Further, heat is a form of energy and ought to be measured in the units of energy (ergs) without reference to a particular substance, such as water, or to any particular temperature. The calorie was a unit invented about a century ago for convenience because the early research work in calorimetry was mostly done by observing the change of temperature of a water bath; to-day, however, electrical heating and measuring are the rule. The Royal Society has now decided, in concert with various international scientific bodies, not to use the calorie any more in its publications but the joule instead (the joule is the name given to 10^7 ergs, and there are 4.1855 joules to each 15° calorie), and scientific journals are expected to follow suit. For a time at least heat values will be given in joules with the calorie equivalent in parentheses afterwards, but it is suggested in the Royal Society's pamphlet that for nutrition studies it may be as well to go on with the old unit, since the general public is calorie-conscious.

DIAGNOSIS OF CANCER

The need for a reliable test for cancer is still as urgent as it ever was, for in spite of intensive research there is still no test which will satisfy all the necessary requirements. A test which has attracted much attention during the last year has been the so-called Huggins reaction[1] (or iodoacetate test), and many workers have investigated its usefulness in the diagnosis and prognosis of cancer.[2-5] Unfortunately the lay press in the U.S.A. reported the original work in enthusiastic terms before it had been properly studied, and the results of careful investigations have since clearly underlined its limitations. Huggins himself never claimed the test to be diagnostic, and indeed various workers have found that the proportion of false-positive results in non-malignant conditions ranged from 35 to 70%. The fact that these figures are higher than those reported by Huggins may be due to the well-recognized difficulty in reading the end-point, though the most recent modification in technique has improved the test.[6] Though Huggins and his colleagues originally claimed that the test was positive in 96% of the cases of malignant disease which they studied, other workers have reported figures in the neighbourhood of 70–80%—an indication of only mediocre accuracy. Furthermore, results are not easily reproducible.

The paper by Dr. Harold Jackson appearing elsewhere in this issue serves to confirm the conclusions of the American investigators about the uselessness and inconsistency of the test. Even to choose between the original and the modified methods is not easy. Jackson preferred the original method, with which he obtained fewer false positives in the normal group. Nevertheless, many of his patients with diseases other than cancer gave positive results (he tested no comparable cases by the modified technique), and most of the other workers prefer the modified method—for instance, in Homburger's[3] cases the proportion of false positives was decreased, though the proportion of false negatives increased. There is no known test for cancer which can claim to be diagnostic, but one other test at least—the polarographic serum test based on the methods of Brdička—does appear to be worth investigating further. In the meantime the best that can be said for the iodoacetate test is that a positive result perhaps gives some indication of an abnormal condition.

[1] Huggins, C., *et al.*, *Cancer Res.*, 1949, **9**, 177.
[2] Bodansky O., and McInnes, G. F., *Cancer*, 1950, **3**, 1.
[3] Homburger, F., *et al.*, ibid., 1950, **3**, 15.
[4] Finnegan, J. V., *et al.*, *J. Lab. clin. Med.*, 1950, **35**, 708.
[5] Gilligan, D. R., *et al.*, *New Engl. J. Med.*, 1950, **242**, 807.
[6] Huggins, C., *et al.*, *J. Amer. med. Ass.*, 1950, **143**, 11.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

MENSTRUAL DISORDERS AND THE MENOPAUSE

I. PHYSIOLOGICAL BASIS AND DIAGNOSIS

BY

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From the menarche to the menopause the endometrium undergoes a series of changes which periodically culminate in uterine bleeding. They consist of growth, secretion, shrinkage, and shedding. This sequence of events depends on the rhythmical rise and fall of ovarian secretion, which is controlled, in its turn, by the cyclical activity of the gonadotrophic hormones of the pituitary gland.

The Menstrual Cycle

The crucial event of the ovarian cycle is ovulation; on it depend not only the release of the ovum but the formation of the corpus luteum and the secretion of progesterone. Before ovulation takes place the endometrium is solely under the influence of the oestrogenic hormone, which stimulates growth and proliferation. After ovulation the combined effect of oestrogen and progesterone leads to glycogen production and secretion of mucus by the endometrial glands, and to conversion of the stroma into the decidua that is essential for the embedding of a fertilized ovum. These changes therefore constitute the prelude to pregnancy and are described as "progestational." Thus we may refer to the pre-ovulatory phase of the endometrial cycle as "proliferative," and to the post-ovulatory phase as "secretory" or "progestational."

Unless conception sets in motion the complex chain of endocrine reactions that leads to maintenance of the corpus luteum, the latter degenerates in due course and deprives the endometrium of the sustaining influence of the ovarian hormones. The premenstrual endometrium is thick, succulent, and oedematous. It is richly supplied with elaborately coiled vessels. Withdrawal of oestrogen results in dehydration, and as the endometrium shrinks the vessels become kinked, engorged, and congested. At the same time withdrawal of both ovarian hormones leads to necrosis of the glands and stroma. This is accentuated by the subsequent ischaemia, which may last for some hours before vasodilatation finally ensues, with rupture of the vessels, haemorrhage, and piecemeal shedding of the superficial layers of the endometrium.

Effect of Oestrogen and Progesterone on Uterine Bleeding

Normal menstruation is due to deprivation of both oestrogen and progesterone. Each of these hormones, however, has a specific effect on uterine bleeding.

The effect of oestrogen is perhaps best explained by the hypothetical conception of the "bleeding threshold" (Fig. 1). Let us suppose that there are three levels of effective oestrogen concentration. (It is important to refer to "effective oestrogen concentration," for this takes into account not only the concentration of oestrogen in the blood but also the degree of endometrial responsiveness to oestrogen.) One of these levels is the bleeding threshold, and whenever the effective concentration of oestrogen lies within this range bleeding will occur. If the effective concentration is below this level, as it is in most cases of amenorrhoea due to a refractory endometrium or to ovarian or pituitary failure, "subthreshold amenorrhoea" will be the result. Normal menstruation is due to oestrogen (and progesterone) deprivations, and consequently to a fall in the effective concentration from superthreshold to threshold levels. Similarly, the administration of oestrogen in cases of amenorrhoea usually leads to bleeding a few days after the course is completed ("oestrogen withdrawal bleeding"), and is due to the drop from superthreshold to threshold levels. On the other hand, bleeding may be arrested if the effective concentration is raised to superthreshold levels with high doses of oestrogen, or if the effective concentration is lowered, either by opposing the action of oestrogen with androgen or by rendering the endometrium less responsive to oestrogen with progesterone.

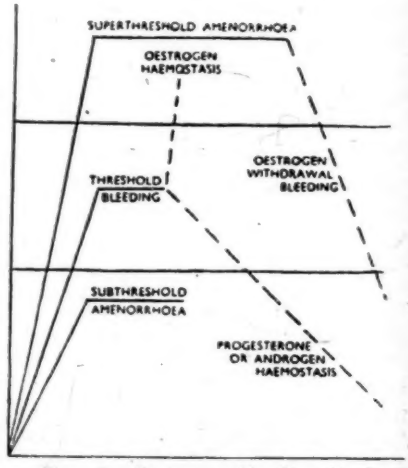

FIG. 1.—Oestrogen bleeding levels.

Though the individual roles of oestrogen and progesterone in the production of uterine bleeding are not clearly understood, something is known of their characteristic bleeding patterns. Oestrogen withdrawal bleeding, for example, is nearly always brief, scanty, and painless. Bleeding can also occur while the endometrium is still under the influence of oestrogen—for instance, in the course of prolonged and continuous oestrogen therapy. Another example is metropathia haemorrhagica, in which ovulation fails to take place and the endometrium is built up, under the constant and unopposed action of oestrogen, to a polypoid, oedematous, and haemorrhagic structure. The resulting bleeding is apt to be prolonged and variable in quantity, sometimes amounting to flooding, sometimes consisting of a mere trickle. These protracted episodes of bleeding are usually associated with incomplete shedding of the endometrium. On the other hand, progesterone-deprivation bleeding from an endometrium previously primed with oestrogen has all the characteristics of a "normal" menstrual period with regard to the duration and amount of loss, and is accompanied by complete shedding of the endometrium.

Mechanism of Ovulation

Rupture of the Graafian follicle and discharge of the ovum are not due simply to the mounting tension on its walls of increasing quantities of follicular fluid, but is almost certainly brought about by the activity of the gonadotrophic hormones. During the early days of the menstrual cycle the follicle-stimulating hormone (F.S.H.)

controls the development of the Graafian follicle, which in due course begins to secrete oestrogen. This, in turn, inhibits F.S.H. secretion, and its concentration wanes. Luteinizing hormone (L.H.) now begins to be elaborated by the pituitary, and ovulation probably takes place only when the falling level of F.S.H. and the rising level of L.H. reach a certain ratio.

Effect of Ovarian Hormones on Uterine Muscle

It is now generally accepted that oestrogen increases the general tone of the uterine muscle and induces relatively frequent contractions of low amplitude, whereas progesterone induces less frequent contractions, but of greater amplitude. Indeed, in some cases the strength of the contraction may exceed the blood pressure in the uterine vessels, giving rise to painful ischaemia of the uterine muscle.

Abnormal Bleeding Patterns

Ovarian failure, according to its severity, gives rise to different bleeding patterns, of which the following are characteristic.

Ovulatory Oligomenorrhoea.—The length of the cycle is increased, though ovulation does eventually take place about 14 days before the onset of bleeding. The prolonged pre-ovulatory phase may be due to inadequate F.S.H. secretion in the early days of the cycle, or failure to achieve the necessary F.S.H./L.H. ratio within the usual period of time. Bleeding is normal in amount and duration when it does appear.

Menorrhagia.—This means heavy bleeding, often prolonged, and sometimes associated with short cycles. Ovulation is usually found to be taking place, though the post-ovulatory phase of the cycle may be shorter than 14 days, and an endometrial biopsy taken on the first day of bleeding may show signs (such as persistence of undifferentiated stromal cells) of inadequate progestational development. Menorrhagia is probably due to slight deficiency of progesterone secretion, so that the endometrium tends to be incompletely shed, with increase in the duration and amount of bleeding. This condition represents the mildest type of ovarian failure.

Metropathia Haemorrhagica.—Here no semblance of a menstrual cycle remains. Episodes of irregular bleeding—sometimes amounting to alarming flooding and sometimes consisting of a mere trickle—may last from a week to several months, and alternate with phases of amenorrhoea of equally uncertain duration. Ovulation fails to take place and the endometrium is under the constant and sole influence of oestrogen. As soon as the endometrium has been built up to a thickened, oedematous, and haemorrhagic structure, irregular shedding takes place, which is incomplete, however, because of the absence of progesterone. Finally, so much endometrium is denuded that bleeding ceases, and once again, under the continuous influence of oestrogen, the endometrium is reconstructed to form an exaggeration of the normal proliferative pattern with widely dilated glands ("Swiss cheese" appearance), reduplication of glandular epithelium, and an oedematous and haemorrhagic stroma.

Amenorrhoea or Non-ovulatory Oligomenorrhoea.—This represents the severest type of ovarian failure. Not only is no progesterone secreted, not only does ovulation fail to occur, but the oestrogen level is too low (or only occasionally high enough) to lead to uterine bleeding.

Other Menstrual Patterns.—The significance of intermenstrual "spotting" is often not apparent. It may result from a fall in the effective oestrogen concentration at the time of ovulation. Though it may be a matter of inconvenience and anxiety to the patient, it is seldom of sinister significance (unless it is due to organic causes) and does not easily respond to available therapeutic measures.

Premenstrual "trickling" may be associated with mild progesterone deficiency, but endocrine therapy is equally ineffective.

Hypomenorrhoea (scanty periods) is usually of no significance. If ovulation takes place the amount of bleeding does not matter, unless it is inconveniently excessive.

Aids to Diagnosis

(1) *History Taking: Menstrual Charts.*—To distinguish clinically between these various bleeding patterns an accurate menstrual history must be taken. This is not easy. The patient is often uncertain of her recent menstrual dates, and is apt to confuse the issue with misleading statements such as, "My periods come every three weeks," when she means that the interval between the end of one period and the beginning of the next is three weeks; or, "I see my periods twice in a month," when she means that one period started on the second day of the month and the next on the thirtieth. The doctor, on the other hand, can usually ill afford the time to unravel this vague and badly expressed story. Even if he succeeds he may still fail to paint a sufficiently vivid mental picture of the bleeding pattern to enable him to make a clinical diagnosis by merely entering a list of the dates of recent periods in the patient's clinical notes. The use of some form of menstrual chart (see Fig. 2) is therefore almost essential to the gynaecologist or endocrinologist constantly dealing with cases of functional menstrual disorder. Even the practitioner, conscientiously determined to understand his patient's menstrual problems, may wish to use such charts in cases of this nature. In spite of one's best endeavours, however, one may fail to make any sense out of the patient's history. In that case, she should be instructed to go home and keep an accurate note of her bleeding dates, and possibly also of her basal temperatures, and bring it back in two months. This period of observation has the added advantage that it prevents officious endocrine therapy in cases in which the menstrual disturbance is merely transient and of no serious significance. Spontaneous remission not infrequently occurs during this time, and unwarranted claims are often made for endocrine therapy administered coincidentally with the onset of a period of remission. On the other hand, if a clear-cut diagnosis of metropathia, for instance, has been made it may obviously be unwise to delay treatment.

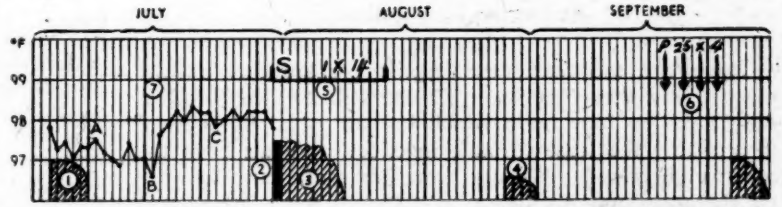

FIG. 2.—Menstrual Chart.* 1. Normal period. 2. Dysmenorrhoea denoted by blacked-in line. 3. Heavy period. 4. Scanty period. 5. Oral treatment for 14 days—stilboestrol, 1 mg. daily. 6. Injection treatment—progesterone, 25 mg., every other day for four injections. 7. Basal temperature records: (A) pre-ovulatory temperature, (B) pre-ovulatory "dip," (C) post-ovulatory temperature.

(2) *Basal Temperature Records.*—There is evidence that the body temperature rises in the presence of progesterone. Thus, if the early morning oral temperature is recorded daily throughout a normal cycle it will show a higher level after ovulation than before (see Fig. 2). This "biphasic temperature pattern" indicates that the cycle is an ovulatory one. Furthermore, it is possible to determine when ovulation takes place—namely, on the day when the

*Menstrual charts of this type (extending over two, four, or eight years) can be supplied by Messrs. Ash and Co., Holyrood Street, London, S.E.1.

temperature rises. Sometimes there is a "pre-ovulatory dip" which heralds the ovulatory rise: indeed, in a few cases, in which the post-ovulatory temperature is not appreciably raised, this dip is the only indication of ovulation.

(3) *Endometrial Biopsy or Curettage.*—In the presence of a biphasic temperature pattern it is practically certain that the cycle is ovulatory. These temperature studies have therefore made it possible to dispense on many occasions with an endometrial biopsy. On the other hand, absence of a typical biphasic pattern does not so surely indicate that ovulation has not taken place. Furthermore, some patients are not intelligent or co-operative enough to take their temperatures accurately, and a biopsy may then be necessary. In any event, it is at least desirable, if not essential, to perform a biopsy or even a thorough diagnostic curettage, especially in cases of irregular, excessive, or intermenstrual bleeding, to exclude an organic cause before embarking upon endocrine therapy. These procedures are of course beyond the scope of the practitioner, though he should know, in explaining to his patient what is involved, that a biopsy can be taken in about 50% of cases without an anaesthetic and with little discomfort. In most cases the biopsy specimen should be obtained on the first day of bleeding.

Endocrine Preparations

Oestrogens

There are too many oestrogenic preparations on the market, and the practitioner will be well advised to select only three or four upon which he can rely. Stilboestrol is probably the least variable in effect, and has been the most widely used. We are therefore more familiar with its therapeutic performance at different levels of dosage than with any other oestrogen. Moreover, it is cheap and highly potent when given by mouth. It has the disadvantage, however, that the lower limit of its toxicity range overlaps the upper limit of its therapeutic range, and nausea and occasionally vomiting will therefore be experienced in some cases, especially if the doses are unnecessarily large. Ethinyl oestradiol is the most potent oestrogen at present available, being 20 to 25 times more effective than stilboestrol. Unless this fact is fully appreciated there is considerable danger of overdosage. It is given by mouth, and, though it is less likely to produce toxic effects, these may occur, especially if the dose is unnecessarily large.

Conjugated equine oestrogens (an extract of oestrogenic material, mainly in the form of oestrone sulphate, from the urine of pregnant mares) constitute a highly active natural oestrogenic preparation (half as potent as stilboestrol) with minimal tendency to produce unpleasant side-effects. Finally, if it should be necessary to use oestrogens in very large doses without any risk of toxic effects, oestradiol benzoate may be administered by intramuscular injection (50,000 i.u. given twice a week is probably equivalent to 2 mg. of stilboestrol daily by mouth).

Progestogens

Progesterone is usually given by intramuscular injection, whereas ethisterone has progestogenic properties when administered orally. No direct comparison of their potencies has been made, but it is usual to give 30 mg. of ethisterone daily by mouth in those cases in which 20–25 mg. of progesterone would be injected on alternate days.

Androgens

It is seldom necessary to use testosterone propionate by intramuscular injection, and methyl testosterone in oral tablets of 10 mg. daily is usually effective for therapeutic purposes.

Gonadotrophins

These compounds have led to disappointing results. Until more potent or effective preparations are available for clinical use the practitioner would be wise to avoid them.

BRITISH ORTHOPAEDIC ASSOCIATION

ANNUAL MEETING, 1950

The annual meeting of the British Orthopaedic Association was held in London on October 26, 27, and 28, under the presidency of Mr. S. L. HIGGS.

Femoral Lengthening in Leg Equalization.—Mr. D. WAINWRIGHT (Newcastle) discussed the problem of leg equalization in such conditions as poliomyelitis, congenital short femur, and premature epiphysial fusion. He considered that femoral lengthening had a definite place in treatment. Twenty-five patients had been operated upon. The average gain in length was two inches. Complications included: delayed union, one case; stiffness of the knee, two cases; and temporary nerve paralysis, two cases. There were no vascular complications. Mr. F. G. ALLAN (Birmingham) agreed that knee stiffness presented a real problem.

Immobilization Osteoporosis.—Dr. HARWOOD STEVENSON (Stanmore) had studied the radiographs of 100 patients submitted to prolonged immobilization for various diseases and had found that the process of osteoporosis followed a typical pattern irrespective of the nature of the primary disease. Osteoporosis developed rapidly and might be obvious within six weeks, but if mobility was maintained disease might be present in a limb for many months without leading to marked osteoporosis. These observations suggested that osteoporosis was a consequence of immobilization as such rather than of disease. Dr. H. A. SISSONS (London) had studied the gross and microscopic structure of bone obtained from osteoporotic limbs and from the site of prematurely fused epiphyses. Examination of trabecular structure was aided by radiographs of thin bone sections. In areas of bone atrophy osteoclasis and osteoblastic new bone formation proceeded concurrently. Hyperaemia was not evident. In sections from areas of premature epiphysial fusion there was disruption of the epiphysis into the diaphysis and bony bridging of the epiphysial line. The evidence suggested that the process of atrophy occurring during immobilization was one of osteoporosis in the strict sense of the word, and was not simply a halisteresis. The process was not due to hyperaemia alone. Mr. H. JACKSON BURROWS (London), discussing the two preceding papers, said that in normal bone there was a continual and balanced process of absorption and laying down of bone. In disuse atrophy there was diminished replacement of bone and increased absorption. The stimulus responsible was unknown. Vascularity had little to do with it. It was noteworthy that a general stimulus might affect only local areas of bone.

Curve Patterns in Idiopathic Structural Scoliosis.—Mr. J. I. P. JAMES (London) recalled that recent work in America had shown that the pattern of the curve in idiopathic scoliosis was the key to the prognosis. He reported a study of the typical features and prognosis in two curve patterns—infantile idiopathic scoliosis and primary lumbar idiopathic scoliosis. In the former the prognosis had been assessed from an analysis of 33 cases. Exceptionally a curve that was initially slight might disappear; a few might remain stationary; but most curves progressed and led to severe deformity. Treatment was very unsatisfactory. Primary lumbar idiopathic scoliosis had a benign course; correction was not required. But pain, developing in middle life from osteoarthritis, was much more common in this than in other patterns of scoliosis. If not relieved by a suitable corset, fusion (without correction) might be required. Mr. H. OSMOND-CLARKE (London) said that although a study of the curve patterns simplified prognosis it did not simplify treatment. Infantile scoliosis was a problem to which no solution was known. All such patients should be segregated in specially equipped clinics.

Experimental Production of Congenital Defects.—Dr. P. K. DURAISWAMI (Liverpool) illustrated experiments in which insulin had been injected into the yolk of fertilized hens' eggs. A high proportion of the chickens developed congenital deformities, which often affected the skeleton (see *Journal*, August 12, p. 384).

Sprung Back.—Mr. P. H. NEWMAN (London) described recent investigations into the pathology of a common clinical type of low back pain characterized by an onset in young adults, often preceded by injury, increase of pain on flexion and relief with extension, local midline tenderness and a palpable depression between two adjacent lower lumbar spinous processes, but with no other objective findings. He believed that the underlying pathology was a disruption of the posterior intervertebral structures by a flexion injury. Healing by fibrosis occurred, but full stability was not regained. Once the back had been sprung painful recurrences might occur whenever the protective extensor muscles were off their guard.

Reconstructive Surgery in Infantile Paralysis

Mr. NORMAN CAPENER (Exeter), introducing a symposium on reconstructive surgery in infantile paralysis, recalled that disability might depend upon many factors which must all be born in mind when approaching the problems of reconstruction. It was important that there should be a full understanding of the applied physiology of muscle and joints if the most efficient use of the remaining muscle power was to be achieved. Mr. J. P. CAMPBELL (Nottingham) discussed the role of soft-tissue reconstructive operations in poliomyelitic paralysis involving the foot and calf. Tendon transplants alone, or as supplements to joint stabilization, were of definite value.

Reconstructive Surgery in Childhood.—Miss M. FORRESTER-BROWN (Bath) recalled that some years ago she had pleaded for the early stabilization of deformed feet in children, but it had been argued against her proposal that either fusion was not obtained or feet so stabilized did not grow. She had found these criticisms to be unfounded, for fusion was in fact obtained, and, provided that only the articular part of the cartilage was removed, growth continued.

Subtaloid Arthrodeses.—Mr. T. T. STAMM (London) reviewed the important part played by tarsal fusion operations in stabilizing paralysed and deformed feet. Any foot could be stabilized by triple tarsal fusion. Because the foot was hinged behind its centre it was usually desirable to displace the foot backwards (as in the Naughton Dunn operation) as part of the triple fusion operation to prevent the tendency for the forefoot to drop downwards. For simple drop-foot the Lambrinudi type of tarsal fusion, in which an anterior wedge is removed from the subtaloid joint, was very satisfactory. Reversed drop-foot or calcaneus deformity was well corrected by a reverse type of Lambrinudi procedure in which most of the bone wedge should be taken from the calcaneum. The late results in 32 cases of tarsal arthrodesis were presented by Mr. A. J. DREW (London). From the point of view of function the results were highly satisfactory, but the appearance of the foot was often less pleasing. There was freedom from pain in 74% of cases.

Elmslie's Operation for the Calcaneus Foot.—Mr. J. A. CHOLMELEY (Stanmore) reviewed the important features of Elmslie's operation for calcaneus deformity of the foot. At the first stage cavus deformity of the foot was corrected by soft-tissue stripping and talo-navicular arthrodesis, and the foot was immobilized in plaster in extreme dorsiflexion. At the second stage the posterior part of the subtaloid joint was arthrodesed through a posterior approach; a longitudinal strip of the tendo Achillis was attached to the back of the tibia to give a tenodesis effect with the foot in 20 degrees of equinus; and the calf muscles were reinforced by transfer of tibialis posterior, flexor digitorum longus, flexor hallucis longus, and peronei longus and brevis to the back of the calcaneum.

In the discussion that followed this symposium Mr. S. A. S. MALKIN (Nottingham) said that two of the greatest problems in the reconstructive surgery of poliomyelitis were paralysis of the gluteus medius and paralysis of the quadriceps. In gluteus medius paralysis he had been dissatisfied with the results of the various tendon transfers. In quadriceps paralysis the merits of hamstring transfers had been the subject of controversy but in his opinion they were of definite value. He did not consider that any reconstructive operation could be regarded as entirely satisfactory unless the need for appliances was reduced or eliminated as a result of the operation. Mr. ERIC LLOYD (London) had studied the late results in two series of cases operated upon many years ago for calcaneus deformity. In the first series the Elmslie operation had been used; in the second the reverse Lambrinudi operation. There was very little to choose between the results in the two series. He considered neither operation should be done in children under the age of 10 years. Mr. H. H. LANGSTON (Winchester) felt that the better care now being given to patients in the early stages of poliomyelitis might reduce the proportion of cases requiring reconstructive operations. Mr. E. S. EVANS (Alton) referred to the use of lumbar ganglionectomy as a means of improving the peripheral circulation and reducing such troublesome complications as chilblains. He considered that ganglionectomy had too often been condemned because too much was expected of it. It was true that the dramatic initial improvement in the circulation was not maintained, but the circulation never returned to a state so bad as it was before operation.

Virus Encephalitis of Mice

Mr. KINGSLEY SANDERS (Oxford) had studied the behaviour of a virus causing encephalitis in mice, with particular reference to its transport and multiplication in the body. Since the lesions produced by the virus, and certain other features of its behaviour, were closely similar to those of the virus of poliomyelitis, he believed that his researches might have a bearing on the transport and multiplication of the poliomyelitis virus itself. In some early experiments encephalitis virus was introduced into a muscle of the lower limb in mice: flaccid paralysis developed in the lower limb muscles of the same side. Similarly, if the sciatic nerve was steeped in a solution containing the virus, paralysis developed in the corresponding limb. In further experiments the development of paralysis after muscle inoculation and after steeping of the sciatic nerve in virus-containing solution was prevented by interruption of the nerve fibres proximal to the application of virus. Any of the methods of nerve fibre interruption—section, crushing, freezing, cauterization—gave protection. These results, taken together, suggested that the virus travelled to the central nervous system along the nerve fibres. Using similar methods it had been possible to assess the rate of travel of the virus along the nerve fibre after its introduction into the muscle or nerve. Proximal travel began almost immediately after muscle inoculation and proceeded at the rate of about half a millimetre an hour.

Multiplication of the virus after its entry into the central nervous system had been studied in the hypoglossal nuclei after injection of the virus into the tongue. The nuclei were examined and assayed for virus concentration at various time intervals after injection. It was thus possible to assess the rapidity of multiplication of the virus. It was found that immediately after arrival of the virus in the central nervous system there was an initial decline in the virus concentration. After a latent period there was a very rapid multiplication of virus concentration. It was further shown that during the latent period virus was still present in the nuclei, and that multiplication depended upon the integrity of the nerve cells.

Miscellaneous Subjects

A Dangerous Type of Fracture Dislocation of the Foot.—Mr. W. GISSANE (Birmingham) called attention to the risk of circulatory arrest in the foot after dislocation of the tarso-metatarsal joints with multiple metatarsal fractures—the Lisfranc fracture-dislocation. He believed that the bone injury was caused by excessive rotational violence rather than by direct violence. He advocated immediate operative reduction, the first step in which should be to secure accurate reduction of the medial and middle cuneiform-metatarsal joints.

Fractures of the Radial Head with Inferior Radio-ulnar Dislocation.—Mr. P. ESSEX-LOPRESTI (Birmingham) described the

features of an uncommon forearm injury of which he had observed two cases. The injury was a comminuted fracture of the head of the radius, associated with upward displacement of the radius relative to the ulna which manifested itself at the wrist by dislocation or subluxation of the inferior radio-ulnar joint. It was caused by a force acting longitudinally in the axis of the forearm. Although the injury was uncommon, its recognition was important, because if the head of the radius was excised the radio-ulnar subluxation was liable to persist or increase. Reconstruction of the head of the radius after reduction of the sublúxation was probably the treatment of choice.

Light Metal Elbow Crutch and Walking-stick.—Mr. F. G. BADGER (Birmingham) demonstrated new types of elbow crutch and walking-stick which have been developed at the Birmingham Accident Hospital.

Pigmented Villonodular Synovitis.—Mr. G. R. FISK (London) had studied six cases of pigmented villonodular synovitis. The condition affected a single joint, usually the knee. It occurred in two forms, generalized and localized. The former was often preceded by injury and was characterized by persistent swelling and effusion of the joint, which might resemble a tuberculous infection. Treatment was by synovectomy, and, provided removal was complete, the prognosis was good. The localized form occurred as a circumscribed nodule, often near the joint line. If pedunculated it might cause recurrent locking of the joint suggestive of a cartilage tear. Treatment was by excision of the nodule.

Actinomycosis of Bone.—Mr. V. ZACHARY COPE (London) reviewed the characteristic features of actinomycosis with particular reference to bone infection. He emphasized the facts that the actinomyces found so commonly in the soil seldom cause human or animal disease and that the causative organism was almost invariably derived from the human digestive tract. The bone most commonly affected was the mandible. In the spine, any area of which might be affected, actinomycosis usually attacked the superficial parts of the bone; but unlike tuberculosis it commonly involved the transverse or costal processes as well as the vertebral body. Collapse of the body was exceptional and the intervertebral disk was resistant to infection, so deformity was slight. Early diagnosis was important; for if left untreated the disease proved fatal within two or three years, whereas if it was treated efficiently by very large doses of penicillin or streptomycin, supplemented by blood transfusion and general therapy, there was a good prospect of permanent cure.

Internal Fixation of the McMurray Osteotomy with a Trifin Nail.—Mr. ROBERT ROAF (Liverpool) had devised a simple method of internal fixation of the femoral fragments after displacement osteotomy of the McMurray type. It consisted in driving a long trifin nail from the tip of the greater trochanter downwards and medially into the upper part of the shaft fragment.

Controlled Pseudarthrosis for Fracture of the Neck of the Femur.—Mr. E. MERVYN EVANS (Swansea) described a method of treatment for ununited fractures of the neck of the femur which was applicable to very frail patients. He recalled that when osteotomy failed to stimulate union of the fracture a relatively painless pseudarthrosis might develop at the site of fracture and might give reasonable function. He had attempted to produce such a pseudarthrosis deliberately by encouraging movement after osteotomy while ensuring fixation and union at the site of osteotomy by internal fixation.

Generalized Bone Decalcification.—Dr. C. E. DENT (London) gave an account of some of the rarer forms of generalized bone decalcification, particularly the uncommon cases of rickets or osteomalacia which were resistant to vitamin D. He considered that the primary cause in all these cases was impaired reabsorption by the renal tubules. In one type there was simply impaired reabsorption of phosphates; in a second this abnormality was accompanied by a lowered renal threshold for glucose with consequent glycosuria; and this merged into a third type in which there was also impaired reabsorption of amino-acids which appeared in the urine (Fanconi type; cystine rickets). These conditions were inherited. A further type, distinct from the above and not inherited, was that in which the renal tubules were unable to make ammonia and excrete an acid urine. Acidosis occurred and calcium might be deposited in the kidneys. The skeletal changes were the same whatever the nature of the tubular insufficiency.

Clinical Demonstration

Clinical cases were shown at the Royal National Orthopaedic Hospital. Mr. D. M. BROOKS (London) showed representative cases illustrating reconstructive surgery in paralysis of the upper limb. Mr. R. J. FURLONG (London) showed some excellent results from digital flexor tendon reconstructions. Mr. A. W. LAW (London) showed examples of cup arthroplasty of the hip and spinal osteotomy. Dr. D. S. MCKENZIE (London) presented patients with congenital short limbs who had been fitted with prostheses designed to accommodate the deformed limb without amputation. Mr. J. I. P. JAMES (London) showed patients with scoliosis treated by correction and fusion, and illustrated typical curve patterns in idiopathic scoliosis.

THE DOCTOR'S DAY AND PAY

A PRE-HEALTH-SERVICE STATISTICAL INQUIRY

Professor A. Bradford Hill, the new president of the Royal Statistical Society, in his inaugural address to that body on November 22 took as his theme the statistical inquiries which he had made during the last ten years on behalf of the British Medical Association into the services given by insurance practitioners under the old National Health Insurance Act, and, more recently, following the setting up of the two successive Spens Committees, into the pre-war earnings of general practitioners and of consultants and specialists.

The description of the selection of samples and testing for bias had its chief interest for the statistical expert; moreover, as the lecturer said, with the advent of the new Health Service much of this work belonged to a vanished world. Nevertheless, the structure of the new era was partly based upon the figures of the old, so that the data had an interest not only for the historian but for the economist and also for all members of the medical profession working in the new Service, especially in view of the inquiries which were now proceeding into practitioners' incomes and practice expenses.

The fixing of the capitation fee troubled the entire course of National Health Insurance. One of the factors taken into account in adjusting it from time to time had been the number of items of service which a practitioner on the average was called upon to provide for the insured persons on his list; but this had proved very difficult to ascertain. The British Medical Association, through the panel committees, had had access to the records of a generous sample of practitioners, and at the court of inquiry in 1937 it brought forward evidence to show that during 1936 the practitioners in this sample had paid an average of 1.33 visits and had had an average of 3.80 attendances at their surgeries for each insured person on their lists, making a total of 5.13 such services. The Ministry of Health disputed these figures and cited the entries made by practitioners on medical record cards, which gave an average of 0.76 visits and 2.90 attendances, a total of 3.66 services, or only some 70% of the B.M.A. figure. The Ministry's figures, however, were admittedly an understatement, because by no means all the services had been recorded on the cards. It was at that point that the lecturer had been called in.

A Random Sample

It might be considered an easy matter to select a random sample from the total list of insurance practitioners and request those selected to keep accurate records for twelve months. But the record keepers would have an onerous task; there would be many refusals to co-operate and many more lapses from co-operation as the year went on. To overcome this difficulty, 6,000 names had been selected at random from the 17,734 insurance practitioners—principals only—and had been divided into 12 groups, each of 500. Each doctor had been asked to keep a record for one prescribed month of the year from July, 1938,

to June, 1939, and in this way, by spreading the groups over the whole year, the calendar was covered, a random sample of the "universe" was obtained for each month, no doctor was assigned too arduous a task, and the total number taking part was sufficiently large, being in fact rather more than one-third of those engaged in the Service.

One point of trivial interest (though perhaps not so trivial in view of the tendency to sample by a selection of surnames beginning with the same initial) might be mentioned. Insurance practitioners whose names began with M had numbered 2,388, or nearly one in seven of the total. The next most-favoured letters of the alphabet, B and S, were far behind, each accounting for only some 1,500 names.

In addition to asking about attendances and visits, five other questions had been asked: (1) the number of special, extra, or night visits; (2) the operations, major or minor, performed; (3) the injections given; (4) the insurance certificates issued, and (5) the reports made. Of the 500 practitioners who had been allocated to each month of the year, each group of 100 had been requested to make an additional return in respect of one of these five items. Every third name had been taken from an alphabetical list of all insurance practitioners and assigned to a month and to one of the five groups. Thus the third, sixth, ninth, twelfth, and fifteenth names had been assigned to January, and to each of the groups in turn; the eighteenth, twenty-first, twenty-fourth, twenty-seventh, and thirtieth to February, and again to each of the groups, and so on.

Of the 6,000 doctors thus selected less than 1% had refused to participate, some because they were too busy and others because they had unprintable views about the B.M.A., the Ministry of Health, or statisticians, or all three; a number of others who had agreed to co-operate had failed to send in returns, and some had fallen out during the year by reason of retirement or death. Altogether the total who had made returns was 5,418, of whom 50% had lists of less than 1,000, while nearly 7% had lists of 2,500 or more. The average list was 1,148, and the number of insured persons covered in the survey was 6,218,752.

Items of Service

In the result the number of attendances per insured person for the year was found to average 3.69, and the number of visits, 1.12, making a total of 4.81 items. This was inevitably an understatement for certain reasons, the principal being that 5% of the 6,000 practitioners had retired or died during the year, and, although their places were taken by other practitioners, the services of these were not counted. On another method of calculation the average of attendances was 4.13, and of visits 1.26, a total of 5.39. The truth evidently lay somewhere between those two totals, 4.81 and 5.39, and sufficiently near to the original (and contested) B.M.A. figure of 5.13 in 1936.

The figures had been worked out for the seasons, months, and days of the week. The trends were well shown—the autumn rise, the fall in Christmas week, the peak during the first three months of the year, and then the downward tendency until the end of the summer. The inquiry into special services had yielded the following result: for every 100 persons for whom the practitioner was at risk the services given during the year were:

Special, extra, or night visits	11
Operations, major or minor	12
Injections	8.5
Certificates (N.H.I.)	139
Reports and correspondence	24

These special services rendered per doctor per week were, respectively, 2.77, 3.00, 2.12, 34.10, 6.02. Monday was uniformly the doctor's busiest day.

The Income of the General Practitioner

In view of the reference, in the inquiries of the Spens Committee, to normal financial expectations of general medical practice in the past, the lecturer had been asked by the British Medical Association to undertake a statistical inquiry into the pre-war earnings of general practitioners. At that time (1945) there were some 21,700 general practitioners according to a card register which had been kept by the Central Medical War Committee, and it was decided to take a one-in-four sample, asking each practitioner to state his professional income (gross and net) for each of the years 1936, 1937, and 1938, based on accounts accepted by the inspector of taxes. The response to this inquiry had been disappointing, and eventually only about 3,000 returns had been collected in a satisfactory form. From these certain eliminations had to be made to give a homogeneous group, and there were left some 2,300 tabulations relating to gross incomes for each of the three years. Those who sought closely detailed comparisons should refer to the *Report of the Interdepartmental Committee on Remuneration of General Practitioners*.[1] Professor Bradford Hill in his address reproduced the gross and net incomes in different age groups for each £200 of income. Below are a few figures:

Gross Incomes in 1936–8 of Male General Practitioners

Income	Ages				
	65 and Over	55–64	45–54	35–44	34 and Below
Under £1,000 ..	154	178	170	284	291
£1,000 to £2,000 ..	174	441	778	1,480	853
£2,000 + ...	56	290	609	928	238

The figures for the net income showed that of the gross amount 37.4% on the average was swallowed up by expenses.

Net Incomes in 1936–8 of Male General Practitioners

Income	Ages				
	65 and Over	55–64	45–54	35–44	34 and Below
Under £1,000 ..	283	449	642	1,138	836
£1,000 to £2,000 ..	96	411	770	1,376	501
£2,000 + ...	4	49	142	172	33

Of the 41 practitioners who were making net incomes of over £3,000, eight had incomes of between £3,500 and £4,000, and four of between £4,000 and £4,500. All these figures concerning income related, of course, to the entire professional earnings of the general practitioner, not to his earnings under National Health Insurance alone.

The Global Sum

It would be recalled that with the coming of the National Health Service the Government abolished the buying and selling of practices. Thus it became necessary for the purposes of compensation to estimate the aggregate capital value involved, and on the assumption that 17,900 principals would enter the Service it was finally placed at £66m. Professor Bradford Hill gave a careful description of the basic calculations.

The first step was to calculate the total gross income of practitioners in 1938, then to take the number of years' purchase applicable to that value, and to add a betterment factor to take into account the increased values between 1938 and 1946. Two methods were taken for arriving at the gross income, one giving a total of £29m., and the other of £26,560,000. A mean figure was taken of £28m., and this was used in the subsequent calculations of compensation. With some 17,560 principals—the adjusted figure—the amount implied an average gross income of slightly less than £1,600 a year, or, deducting practice expenses, a net income of about £1,000 in the immediate pre-war years. One point which would be noted from the figures was that even at the age of maximum earning capacity (35 to 54) 42% of the net incomes recorded were below £1,000 a year.

Professor Bradford Hill spoke of the practitioners who refused, or, at all events, failed, to send in returns. He speculated on what motive might lie behind refusal to co-operate. "If doctors with small incomes deliberately withheld information, fearing to prejudice the future, how greatly they erred! Let it be a warning to all who neglect for ulterior motives to return their *questionnaires*." At all events, the Spens Committee had found the figures sufficiently accurate for its purpose.

[1]Cmd. 6810. H.M.S.O., 1946.

The Income of the Specialist

In the latter part of his address Professor Bradford Hill turned to the more difficult inquiry into specialist income—more difficult because there was no list of persons who before the war were engaged exclusively or predominantly in consultant or specialist practice. This had been overcome with the help of the secretaries of voluntary hospitals and medical officers of health, and some 6,000 names were obtained of those who must be asked whether they were exclusively or predominantly engaged in consulting and specialist practice in 1938–9. Professor Bradford Hill gave an account of the various precautionary measures which were taken to ensure reliability in what he called "survey work in its most dangerous and treacherous form—that of inquiry by *questionnaire*." Many eliminations had to be made, as was foreseen, of those who were not exclusively engaged in consulting and specialist work. There were also a considerable number of refusals, most pronounced in the oldest age group of 60 and over.

Again the more detailed results were set out in the *Report of the Interdepartmental Committee on Remuneration of Consultants and Specialists*.[1] The tables given in the presidential address were not exactly in the same form as to age groups in the case of consultants and specialists as in the case of general practitioners, but the following extracts from them are of interest:

Gross Incomes in 1938–9 of Male Consultants and Specialists

Income	Ages				
	60 and Over	55–59	45–54	35–44	34 and Below
Under £1,000 ..	32 (9)	16 (1)	12 (2)	53 (6)	68 (15)
£1,000 to £2,000 ..	41 (15)	48 (13)	108 (24)	165 (33)	82 (17)
£2,000+	79 (10)	114 (12)	343 (58)	390 (63)	78 (17)

The figures in brackets indicate those who were not exclusively engaged in specialist and consultant work, although that was their predominant interest. This was a relatively small group in the sample—about one-sixth of the total number—and not actually relevant to the problem under study. These persons did not appear in the other tables.

The figures for net incomes were as follows:

Net Income in 1938–9 of Male Consultants and Specialists (Exclusively Engaged in Such Practice)

Net Income	Ages				
	60 and Over	55–59	45–54	35–44	34 and Below
Under £1,000 ..	55	41	60	119	106
£1,000 to £1,500 ..	24	31	86	113	57
£1,500 to £2,000 ..	18	37	78	109	32
£2,000+	50	69	240	263	32

From these net figures it could be seen that nearly one-third of those consultants and specialists who were at the peak of their earning capacity—namely, the age period of 45 to 54, had a pre-war income of under £1,500, after deduction of practice expenses. At the other end of the scale, however, there were glittering prizes to be won, though not so very many of them. One-sixth of the consultants and specialists of the same age period—that is, 45 to 54—had a net income of £4,000 or more. Taking all ages together, 10 had a net income of over £10,000. In four of these cases the income was between £10,000 and £11,000; in three, between £11,000 and £12,000; in two, between £14,000 and £15,000, and in one, between £15,000 and £16,000.

A comparison with general practitioners on this ground of remuneration was instructive. At the most productive age period of 35 to 54, less than 10% of general practitioners had a net income of £2,000 or above, whereas very nearly half the consultants and specialists reached that level.

Of the specialties of those participating in this inquiry, 23% were surgery, 18% medicine, 10% ear, nose, and throat work, and 15% ophthalmology.

[1] Cmd. 7420. H.M.S.O., 1948.

Practice Expenses

An interesting point arose concerning the practice expenses of general practitioners and consultants and specialists respectively. The tables again were not set out in exactly comparable form. Just over 2,400 incomes of general practitioners out of a total of nearly 7,000 showed practice expenses between 30 and 39% of gross income. Some 1,900 were below and some 2,600 above that level. The numbers included practitioners with and without assistants. Of some 1,600 consultants and specialists, just over 1,000 returned their expenses as between 15 and 34% of gross income. In 120 the expense ratio was below that range, and in about 470 above it. In the case of general practitioners with smaller incomes—below £1,500—the expense ratio was higher. Of 3,000 incomes of general practitioners falling within that income range, 1,200 returned practice expenses as absorbing 40% or more.

Professor Bradford Hill concluded his survey by pointing out that the inquiries, of course, fell within a narrow field. He himself was interested in their content because he had lived all his life with doctors and was interested in their ways of living and thinking. Yet he felt that such field inquiries held also something of general interest to the economist and statistician.

THE DEVELOPMENT OF MICROBIOLOGY

FIRST LEEUWENHOEK LECTURE OF THE ROYAL SOCIETY

The first Leeuwenhoek Lecture of the Royal Society was given on November 9 by Sir PAUL FILDES, lately director of the Medical Research Council's Bacterial Chemistry Research Unit at the Lister Institute. He spoke on "The Development of Microbiology." The Leeuwenhoek Lecture, to be given annually in the field of microbiology, has been established as a result of a legacy to the Society by the late Mr. G. H. Gabb, "the father of the scientific antiquaries" in his own description, whose collection of old instruments was begun as long ago as 1885 and is now in the National Maritime Museum. In accordance with the terms of the bequest, a portrait of Antonj van Leeuwenhoek was displayed to the audience during the lecture.

It was through a series of letters to the Royal Society, published in the *Philosophical Transactions*, that Leeuwenhoek's discoveries were made known. He described the appearance of green algae, rotifers, ciliate protozoa, and bacteria—the latter in 1676 in his eighteenth letter. "My method," he wrote, "I do not impart to others"—and it is still a problem how with a simple microscope, and magnification by 250, he managed to see bacteria. It has been suggested by Dobell that he may have used some form of dark-ground illumination. That he did see them is proved by his account of micro-organisms which, from the conditions of the experiment, must have developed under anaerobic conditions. They were seen in pepper during an attempt by Leeuwenhoek to discover what made pepper hot.

Leeuwenhoek viewed his "little animals" as one might watch the antics of a puppy, and took pleasure from "this new world known to himself alone." He felt a community with them, and wrote that "all the people in the United Netherlands are not so many as I carry in my mouth this very day"—an allusion to the dental scrapings from which so much of his material was obtained. He was elected a Fellow of the Royal Society in 1680, although he was a foreigner, had never attended the meetings of the Society, and was a tradesman (a draper of Delft, in Holland) at a time when the independence attributed to "gentlemen, free and unconfined" was considered a valuable qualification. He was also one of the first working scientists to take exception to casual visitors. He saw visitors only by appointment, and showed them a set demonstration which he kept available for the purpose. To Linnaeus, in 1767, bacteria were "a dubious species under the Order Vermes, Class Chaos"; and the long interval—more than one hundred years—before they were again observed with certainty was a measure of Leeuwenhoek's greatness.

By the beginning of the eighteenth century the study of the very small (but not including bacteria, apart from Leeuwenhoek himself) had become so prevalent among the new philosophers that supporters of the old were moved to object. In its later development from simple interest towards a modern science the course of microbiology was largely influenced by three controversies—on spontaneous generation, on fermentation, and on infectious diseases—of which the first provided the foundation of much of present technique. The use of heat for sterilization, for example, goes back to the work of Spallanzani in the eighteenth century; while, as a survivor of the opposite viewpoint, Charlton Bastian remained until well into the twentieth century as a supporter of spontaneous generation. Through Pasteur, and particularly his work on fermentation and a disease of cultivated silkworms, micro-organisms were recognized by men as factors associated with their daily lives. From his hint to Lister there developed the great contribution of the latter to the controversy on infectious diseases, in which the technical advances introduced by Robert Koch were to make possible more extended progress. The overall effect has been to increase the span of human life—and microbiologists working to-day may be excused for forgetting how recent is their subject.

In his introduction to the lecture—with microbiology presented as a single subject—Sir Paul Fildes referred to the link which had been provided by biochemistry between the separate branches of bacteriology, protozoology, mycology, and even virology. Proceeding, now, to the discovery of bacteriophages by Twort and d'Hérelle, he gave as their distinguishing quality the fact that they were too small to house more than a fraction of the enzymes needed for their multiplication. Reviewing the sequence of size seen in the newest of Leeuwenhoek's protégés, he pointed out that the larger viruses tended to be indistinguishable from bacteria, and the smaller to be akin to "substances." Were viruses living at all? Yes, but like all living things they were composed of lifeless chemical substances. "It is the arrangement that counts to give the attributes of life."

In conclusion, he recalled the eightfold increase in population which had taken place since the beginning of the eighteenth century. Interference with the normal relationships of two biological groups, man and micro-organisms, had produced a set of political difficulties: their solution, through a greater production of food, depended on a greater use of microbiology for this further purpose.

The lecture was illustrated by a film, made by Professor R. J. V. Pulvertaft, showing some of the vast and varied activity of micro-organisms which Leeuwenhoek had so much enjoyed. Water from St. James's Park provided the fauna for one sequence.

The enterprising Department of Student Health at Queen's University, Belfast, has issued its second annual report covering the academic year 1949–50. In addition to a general account of the year's work and details of the clinical findings in the students examined there is a survey of the living conditions of first-year students. All the first-year students (558) at the university had a routine examination which included mass miniature radiography of the chest. One case of active pulmonary tuberculosis was found and 42 inactive cases. Mantoux testing was carried out on 496 of these students, and the negative reactors were offered B.C.G. vaccination. In all, 125 were vaccinated, with 100% conversion and no untoward reactions. In addition to the special first-year examinations, the students of all years had their chests *x*-rayed (it is remarkable to learn that there were no defaulters from this examination). Out of 2,477 examined, there were 7 cases of active pulmonary tuberculosis and 185 inactive cases, of which 151 were healed primary lesions. A large number of students consulted the medical officer during the year, sometimes on their own initiative and sometimes after reference from their doctors. Great care was taken to establish cordial relations with the local practitioners to prevent any misunderstanding about the nature of the student health service, and as a result there was a fruitful co-operation between the medical officer and his professional colleagues.

Reports of Societies

MANCHESTER MEDICAL SOCIETY

INAUGURAL MEETING

The amalgamation of all the existing Manchester medical, surgical, and allied societies into one society, originally suggested 31 years ago, was finally fulfilled at the inaugural meeting of the Manchester Medical Society on October 4.

In the afternoon the first president of the new society, Mr. WILSON HEY, gave his inaugural address on "The Story of the Manchester Medical Societies" in the presence of the vice-chancellor of the university, the Lord Mayor, the Presidents of the Royal Colleges of Surgeons and of Obstetricians and Gynaecologists, the representative of the President of the Royal College of Physicians, the President of the Royal Society of Medicine, the President of the Liverpool Medical Institution, and about 500 Fellows of the new society.

Mr. WILSON HEY, after welcoming the distinguished visitors, described the development and influence of the various medical, surgical, and allied societies in Manchester from the time of the Literary and Philosophical Society in 1781, which was almost entirely medical in character. In 1834 the original Manchester Medical Society was formed with 91 members, while to-day there are approximately 1,000. A hundred and seven years ago its Transactions were printed in the *Provincial Medical and Surgical Journal*, now the *British Medical Journal*. Later they were continued in the *Medical Chronicle*, which was published 1884–1916. After various residences the society moved to Owens College, now the Victoria University of Manchester. The library had incorporated with it the university departmental libraries, and was the largest in the country outside London: it had almost 100,000 books. In 1929 it was given to the university and now every member of the society had the privilege of using the other libraries in the university.

In 1879 the microscopical section of the society was formed, but six years later it was apparent that the microscope dealt with only a minute part of pathology, and consequently an independent pathological society was formed and had flourished until the present day.

The president then referred briefly to the formation of the old Clinical Society (which had ceased to exist in 1925), the Surgical Society (founded in 1922), the Society of Anaesthetists, the Obstetrical Society, the Dermatological Society, the Ophthalmological Society, the Otolaryngological Society, the Odontological Section, and numerous others that had developed from these or been founded by Manchester men. In all, Mr. Hey said, 22 medical societies had thus been formed.

Amalgamation, which had first been suggested in 1918 but for various reasons postponed, was now achieved. The new society had taken its pattern from the Royal Society of Medicine, each of the old societies becoming a section with its own president, who was *ex officio* a vice-president and an honorary secretary of the society. There was only one honorary treasurer, and for the first time there was a whole-time paid secretary. Monthly diaries were being issued, and soon the society would have its *Proceedings and Transactions*.

Plans for a General-practitioner Section

The general practitioner was the chief thought of the council of the society, and it had the formation of a special general-practitioner section in mind. The percentage of practitioner members of the various societies which had now amalgamated had diminished as a result of the Acts of Parliament which came into force in 1911 and 1948; they had converted the practitioner into a "form-filling, regulation-bound doctor." This decline had been assisted by two wars and to some extent by the intermittent postgraduate classes.

Addresses of Welcome

Colonel S. P. DAWSON, Lord Mayor of Manchester, expressed his pleasure at being present and congratulated the president

on his address; he spoke about the admission of women to the earlier societies, and then wished the society every success.

Sir JOHN STOPFORD, vice-chancellor of the University of Manchester, referred to his close and long association with the old society and the university, and also to the 80 years' association of Owens College, later the university, with the Medical Society. In his positions as vice-chancellor, as chairman of the joint advisory board, and as chairman of the Manchester Regional Hospital Board he had excellent opportunities to be thrilled by the new things that he saw happening in medical research and medical education. He referred to the great need and opportunities for even closer co-operation than at present between all branches of medicine, including general practice.

Lord WEBB-JOHNSON, President of the Royal Society of Medicine, London, had no need to remind Fellows of his close association with the Manchester Medical School. After telling his audience about the formation of a new section of general practice in the Royal Society of Medicine, he announced that he had the honour to bring to the Manchester Medical Society greetings from the President and the Council of the Royal Society of Medicine on behalf of its 9,000 Fellows. Thus speaking, he presented to the President of the Manchester Medical Society an illuminated parchment which said:

"The President and Council of the Royal Society of Medicine, on behalf of its nine thousand Fellows, extend Greetings to the Manchester Medical Society on the occasion of the reconstitution of the Medical Societies of Manchester as the Manchester Medical Society.

"The greetings of the Council of the Royal Society of Medicine are the more cordial since the Manchester Medical Society, in uniting an important group of Medical Bodies with similar Objects, has followed the principles which guided the Royal Medical and Chirurgical Society, when in 1907 it happily brought about the fusion of most of the leading Medical Societies of London to reconstitute itself as the Royal Society of Medicine.

"The history of the Royal Society of Medicine since that date gives its Council great confidence in wishing the Manchester Medical Society the greatest possible success in its future life and development. The Royal Society of Medicine is proud to think that it has contributed by example to the formation of a Body whose bright future cannot stand in doubt and whose constitution has been moulded on that of the Royal Society of Medicine.

"It is hoped that, in the abundant activity which will undoubtedly characterize the life of the Manchester Medical Society, place may be found for frequent and friendly liaison with the Royal Society of Medicine.

Webb-Johnson	*President*
A. T. M. Wilson, J. C. Ainsworth Davis	*Honorary Secretaries*
Geoffrey R. Edwards	*Secretary.*"

This totally unexpected and very kind thought of the President and Council of the Royal Society of Medicine gave the greatest pleasure to the President and Fellows of the Manchester Medical Society.

Sir CECIL P. G. WAKELEY, President of the Royal College of Surgeons, brought the congratulations and best wishes of the Royal College of Surgeons and said how pleased he was to come again to Manchester.

Professor HILDA LLOYD, President of the Royal College of Obstetricians and Gynaecologists, offered the best wishes of her College and referred to the admission of women into the societies. She paid tribute to the excellent work of Manchester medical men and women in obstetrics and gynaecology.

Professor CRIGHTON BRAMWELL, on behalf of the President of the Royal College of Physicians, brought the hearty congratulations and best wishes of that Royal College.

Dr. DAVID JOHNSTON, President of the Liverpool Medical Institution, concluded with his best wishes and referred to the close liaison between the Liverpool Medical Institution and the Manchester Medical Society in the past in the organization of the annual joint meetings that had been such a source of pleasure and good will to all.

In the evening the president and Mrs. Hey received the Fellows, guests, and visitors at the society's reception in the Whitworth Art Gallery (by the kind permission of the governors) and thus concluded a most happy and successful inauguration of the new Manchester Medical Society.

Correspondence

Displaced Registrars

SIR,—Publication of the circular from the Ministry of Health (*Supplement*, November 18, p. 204) regarding the drastic reduction in numbers of middle and senior registrars employed in the hospital service must have struck a chill into the heart of many a doctor. At the same time this grim document must surely have roused the fighting spirit of those most threatened by its high-handed phrases and dictatorial statements. Let it be hoped that that fighting spirit will not be stilled by further idle promises or sops, which no doubt will in due course be handed out to hundreds of highly trained doctors who will shortly be unemployed.

Let there be no mistake: no one will save those so threatened but themselves, and only concerted action can spare us from a plight which will cut across the path of human endeavour, waste years of highly trained skill, breed bitterness, disillusionment, and frustration, and deprive the hospital service and teaching centres of the country of assistance which they can ill afford to lose.

Feelings of sympathy and even of anger and disgust have been expressed by our chiefs and teachers, who have endeavoured to place us by their strong support in posts which they feel we merit by dint of long training and experience in general medicine or a special branch. For this support and encouragement we are grateful, but it is not enough. Nor have we the right to expect our sponsors to fight our battles for us to the end. It is up to us to fight the toughest and final engagement ourselves before it is too late and we are overwhelmed without even the sign of a struggle.

All are agreed that heavy reduction in the numbers of registrars must be made unless the Government can appreciate that further expansion of consultant services is needed in the public interest. No fair-minded person, however, could agree that the precipitate dismissal of large numbers of highly trained young specialists is either just or sensible, and an economy axe falling on medical skill would be the greatest tragedy in the development of the National Health Service. Before it is too late and doctors who are recognized to be worthy of consultant status are dismissed the Service wholesale, three questions should be asked and faithfully answered by all who are concerned in this crisis:

(i) Will the care and standard of the treatment of the patient suffer?

(ii) Will undergraduate or postgraduate teaching be in any way impaired, either in the opinion of those at home or abroad, whence hundreds of doctors come to our shores for instruction?

(iii) The pursuit of some form of clinical research should be regarded as an essential part of the training of any consultant, and at the present time the field of opportunity that offers itself is wide. Will the high standard of medical research carried out in our great hospitals fall off, with fewer opportunities for trainee consultants, because of lessened research activity from reduced numbers, and because directors of research units will be deflected from the path of original thought and action by unending routine work, a surfeit of teaching duties, and the frequent calls of more direct clinical responsibility?

If these questions can be answered by an honest "no" by those whose opinions we respect and by those responsible for our fate, then we must submit with good grace, but with bitter disappointment in our hearts, and fade quietly from the scene. If, on the other hand, the answer to any of these issues—and particularly the first—is in the affirmative, and this verdict is expressed by any body of opinion, either public or professional, then the Ministry of Health's policy should be amended forthwith, and registrars should fight hard to see that it is.

It is suggested that registrar groups throughout the hospital service, particularly in the teaching centres, should meet as a matter of urgency and pass their own verdict on the points raised above, and on any other important issue they consider likely to lead to amendment of the circular. Contact with

hospital groups can soon be established if people are really concerned about their fate, which otherwise appears to be sealed. Besides, when a man knows he is to be hanged in a fortnight, it concentrates his mind wonderfully.

The opportunity will not recur, and the sands are running out. The need of doing, therefore, is pressing, since the time of doing is short.—I am, etc.,

London, W.12. DAVID LEWES.

SIR,—The position with regard to registrar appointments is in need of clarification, and an administrative problem of considerable magnitude undoubtedly exists. We and our colleagues are anxious to do all we can to assist the Minister in arriving at a reasonable solution, and have certain suggestions to offer which are outlined below.

Having stated this, we are unable to refrain from expressing our surprise and disgust at the cynical manner in which the memorandum is worded (*Supplement*, November 18, p. 204). We refer in particular to para. 12 of the document, which manifestly expresses direction of experienced medical men.

Furthermore, we wish to state with full emphasis, and in the light of our long collective experience of the working of large non-teaching hospitals, that it will be impossible to prevent an important deterioration in the standard of medical care of hospital patients if these essential members of the medical staff are displaced. We regard the senior registrars and registrars as the backbone of the hospital service in the day-to-day care of the patients.

We offer the following suggestions:

(1) The necessary reduction in establishment for registrars should be reached gradually without hardship to individuals by allowing posts to become vacant at the termination of the normal tenure of the holder. Many of these registrars at present are men of over 35, with family responsibilities, whose careers have already been set back five or six years by war service.

(2) We recommend the creation of a new grade of assistant consultant, with a salary scale intermediate between that of consultant and senior registrar.

(3) There is a great need for the preparation of a scheme whereby men with some hospital experience can be absorbed into general practice at a level justified by their special training if it is found that they are unable to proceed further in their specialist career.

—We are, etc.,

London, N.19. CECIL D. COYLE.
T. ST. M. NORRIS.
H. E. S. PEARSON.

SIR,—In this slow and painful initiation of the Health Service it is to be deplored that sudden changes of policy should occur. Under conditions of war remustering from "trades" which became redundant was accepted in the fighting services as a necessary evil. Under the present circumstances, however, there can be no excuse for the abrupt decision to reduce the registrars of this country by nearly half.

Surely it is fatuous to suggest that the newer trained registrars can acquire, in the four years suggested, the knowledge and the experience which many of us have been gradually acquiring over a period of six, ten, or even more years. Specialties are becoming progressively more advanced and cannot be learnt except by years of careful apprenticeship. Furthermore, after all these years most of us are quite unfitted to revert to general practice.

If the Government has made the unfortunate mistake of training more specialists than it requires it would seem penalty enough for the unfortunate victims to be sentenced to a long spell in the top registrar grade. The rate of pay is certainly not enough to satisfy these people, who have not attained these positions without much toil and sweat.

If the number of registrars is to be reduced, it is only fair that this should be done gradually. Now that we know, for the first time, that the number of consultants is not to be increased, it will not be long before there are less registrars. But meanwhile fully qualified and fully trained men—on whom the State has expended vast sums of money—should surely not be sacked so that more can be trained.

It must be conceded that an annual review of all registrars is a reasonable method of ensuring that their work reaches a satisfactory standard. Apart from this I consider it quite intolerable that any registrar should be directed to relinquish his appointment.—I am, etc.,

Nottingham. CYRIL C. SLACK.

SIR,—The imminent reduction in the registrar establishment prompts us to make the following observations, for we believe that this action, said to be in the interests of the registrar class, is, in fact, contrary to their wishes.

(1) Registrars are prepared for each to be in open competition with his fellows, believing this to be the most certain method of determining the individual best suited for selection to consultant status. He is willing to accept the risk that no consultant post may be available for him on completion of his registrar appointments, but believes that, the better doctor he can become before entering either general practice or some special branch of the Service, the better for the future efficiency of the Service.

(2) The decision who will become consultants will in future be made too soon after qualification—i.e., before there has been adequate time for all-round experience to be gained, or assessment of his capabilities to be made.

(3) The registrar is at present vital in a service which deals not only with the training of consultants but also with the treatment of patients. The long-term consultant establishment problem may be solved by a 40% reduction in the hospital registrars, but this will be accompanied by a reduction in the efficiency of the Service. A great deal of the large volume of work at present being done by registrars will in future have to be done by senior house-officers who are not qualified to do so. If they are sufficiently qualified they should receive the salary of a registrar.

We consider that it is against the democratic traditions of this country that an irrevocable decision affecting a large segment of the medical profession should be made without any reference to their views on the subject. We would suggest, therefore, that hospital residents and registrars throughout the country should meet to decide their attitude to this proposed change and that the Minister should thereafter take a referendum of their views.—We are, etc.,

Bradford.

D. P. GORDON.
R. C. GLEDHILL.
T. G. EVANS.
J. B. WILSON.
J. BRECKENRIDGE.
T. R. DAVISON.
J. M. B. MUIRHEAD.
A. R. WEBSTER.
M. ROSEN.
A. M. EMMERSON.
D. C. SIMPSON.
R. M. DEAN.
H. MICHAELSON.
P. PRATT.
W. S. LOCKE.
G. BRADSHAW.
W. BARUCH.
H. A. KARRACH.
H. A. BARKER.
D. F. O'NEILL.
D. H. MCMILLAN.
M. B. TAYLOR.
W. P. FULLERTON.
D. A. L. DICK.
D. MATHIESON.

Beds for the Tuberculous

SIR,—There are at present approximately 11,000 cases of pulmonary tuberculosis awaiting admission to sanatoria, and many of these will have to wait six to twelve months for a bed. The Minister of Health stated in Parliament on July 27, 1950 (see *Journal*, August 5, p. 371), that on December 31 last 5,000 beds suitable for tuberculous patients were unoccupied, 4,000 being closed for lack of staff.

It must be true of every sanatorium that there are several patients who are retained in the sanatorium longer than is medically necessary because of difficulties connected with their disposal, such as overcrowding and the need for rehousing, the presence of uninfected children in the house, or lack of any home to go to in the case of people who live in lodgings. These patients do not require nursing, as they are invariably up all day, and, in effect, they are mere lodgers in the sanatorium until the difficulties connected with their disposal can be overcome. They are, however, blocking urgently needed beds for

patients requiring active treatment, and they should not, therefore, be accommodated in a ward which is staffed and equipped for treating active cases. All sanatoria with empty beds should make some of these available for this type of patient, and this can be done without materially increasing the demands on the existing staff, as these patients are fully able to make their own beds and keep their room clean and tidy. This annexe system is already a feature in some sanatoria, and provides a valuable link between full institutionalization and a return to the outside world.

An extension of this system to all sanatoria with empty beds would seem to be an immediate practical possibility and should be put into effect forthwith, for every bed counts and time is not on our side.—I am, etc.,

Leeds. M. B. PAUL.

When is Disablement Not Disablement?

SIR,—A patient, a factory porter, having taken much advice about a prolapsed disk, wearing a heavy brace, has been kept by me on the sick list for some months. He is on the Ministry of Labour disabled list and has been seeking sedentary work for some time. He was examined on October 17 and again on November 2 by persons from the Divisional Medical Officer's Department and was informed on November 10 that he was struck off sick pay from November 3. There is no dispute about the medical aspect of the case, he is fit for light work.

Now I have two patients on the sick list, one a professional pianist who has lost two fingers of each hand (not due to an accident), whose corns prevent him from digging. He is, however, fit for light work such as holding horses' heads and acting as a shop steward. Do I sign him off?

The other is an agricultural worker whose feet are crippled with rheumatism. He has a good head for "the odds" and would do well as a bookmaker's clerk (sedentary). There are no bookmakers near. Do I sign him off as fit for work?

One can think of many such cases which my colleagues may have. What, Sir, is your advice?—I am, etc.,

Cricklade, Wilts. T. R. THOMSON.

Problem of the Therapeutic Convulsion

SIR,—In his article (November 11, p. 1092) Dr. T. D. Power suggests that there may be a reversal of psychic evolution and a reliving of past experience during and after therapeutic convulsions.

The following observation may be of interest. I am at present treating with deep psychotherapy a patient who received a concentrated course of E.C.T. eighteen months ago (12 fits in ten days). During the earlier weeks of my treatment when referring to the period of shock therapy she said, "It was like dying and being born again," but she had complete amnesia for the whole of the ten days. After about three months' psychotherapy she said that she could remember one occasion when she was obstinately refusing to get into a bath. After a further period of about ten sessions she suddenly said, "I was in Australia all the time I was having E.C.T.," and she elaborated this with a description of some of the scenery. Australia was in fact the scene of several of the happiest years of her early childhood.

This was her most recent reference to the subject, so that it is at present impossible to state what further fantasies occurred at the time. However, one may legitimately conclude that it is in some cases possible to penetrate the post-E.C.T. amnesia in the same way that one does a childhood amnesia, and that such an exploration may confirm Dr. Power's suggestions on the psychological effects of convulsion therapy.—I am, etc.,

Oxford. OLIVER LYTH.

SIR,—The attention drawn by Dr. T. D. Power (November 11, p. 1092) to the relevance to psychiatry of the teachings of Hughlings Jackson is most welcome, and may herald the adoption of that unity of concept the absence of which has been deplored in recent correspondence (see November 4, p. 1057, and earlier).

It is significant that E.C.T. is only efficacious in certain mental illnesses—viz., acute mania, depressive states, and, to a lesser extent, in paranoid states and in schizophrenia. It is of no value in hysteria, anxiety states, and obsessional neuroses.

The manifestations in mental illness can be ranked in order according to the distance in consciousness at which they arise. Hysterical disorders lie so close to consciousness as to arouse a frequent suspicion of malingering. Anxiety states spring from deeper layers of the mind and their causative factors are rarely so obvious. The symptoms of acute mania and of the depressive states are even less compatible with normal mental functioning and come from deeper levels. At a greater distance still from consciousness, there is the schizophrenic series, ranging from the paranoid cases with fair preservation of the personality, through paraphrenia, to those forms showing great disintegration of personality and eruption of the contents of the unconscious into consciousness. Thus there can be traced from hysteria to schizophrenia a progressive extent of failure of repression, and in the reverse direction an increasing success of integration.

It would therefore appear that E.C.T. is capable of restoring integration at certain levels of the mind, not at more superficial levels, and not at the deepest levels, but at those middle levels whence spring the symptoms of mania, melancholia, and the paranoid group. These divisions recall Hughlings Jackson's teaching that the central nervous system is organized in three levels. The lowest level from the tuber cinereum to the conus medullaris contains centres representing the body in detail. The middle level comprises the Rolandic area where the parts of the body are re-represented. The highest level he places in the prefrontal lobes, and here he assumes concomitance of psychical states with the nervous states of at least the highest layers of this level. They are the physical basis of mind.[1] Jackson does not understand "unconscious states of mind"; for him mind and consciousness are synonymous, although he allows that there may be activities in lower layers of the highest centres without attendant psychical states, which yet lead to activities of those layers whose activities do have attendant psychical states.[2] In the light of our later knowledge of psychopathology his doctrine of concomitance may perhaps be taken further than he felt was warranted.

Physical methods of treatment of the more superficial mental disorders, the neuroses, produce dissolutions in the highest nervous levels—e.g., narco-analysis, continuous narcosis, modified insulin treatment. For the deepest disorders of the mind, the schizophrenias, we use insulin coma, in which partial dissolution is carried as far as Jackson's lowest level. At the middle levels E.C.T. is used to produce a temporary dissolution.

Dissolution at any level is not necessarily complete: Jackson speaks of local dissolutions in connexion with the insanities.[3] This concept can be most usefully applied in diagnosis, with its corresponding implications for treatment. Mental illnesses do not occur in pure form, and in most cases symptoms can be found arising at different levels. The best example of this is the psychoneurotic or reactive depression which one day presents as a depressive state and the next day impresses the clinician with its wealth of neurotic features. The adoption of a "more-or-less" attitude rather than one of "either-or" leads to better understanding and treatment.

This brief note by no means exhausts the possibilities of applying Jackson's concepts to psychiatry, and it is hoped that Dr. Power's article will stimulate others to similar studies.—I am, etc.,

Nottingham. W. L. JONES.

REFERENCES

[1] Taylor J. (editor), *The Selected Writings of John Hughlings Jackson*, 2, 424, London, 1932.
[2] Ibid., 2, 85.
[3] Ibid., 2, 77.

Antihistaminics for Enuresis

SIR,—Dr. D. Hubble's very helpful article (November 11, p. 1108) prompts me to report our experiences with the antihistaminics in this disorder. A proportion of cases of enuresis present a superficial resemblance to allergic disorders in that intervals of freedom vary considerably and relapses are often associated with emotional upset, certain articles of diet, change of climate, etc.

On this analogy I first made some trials with "benadryl" some three years ago, and have found that at least 60% of cases show immediate and progressive improvement. The average dose used for children between 3 and 5 years old is benadryl 20 mg. thrice daily. Other antihistaminics are also effective.

In a single practice far less experience is gained with adult enuresis, but we have a lad of 17 who averaged five wet beds a week and now keeps dry by taking one tablet of "thephorin" daily; he relapses at once if he stops the treatment.

We have also a woman, now aged 27, who averaged five wet beds per fortnight. She was treated most thoroughly with the usual drugs for some eight months and did not improve beyond two lapses per fortnight. As soon as she began to take benadryl 50 mg. three times a day she improved to about one lapse per two months; in spite of trials with other antihistaminics she has maintained this state for the past two years. She is now taking "phenergan" 25 mg. at night and is well satisfied with the improvement.—I am, etc.,

Bath. CHARLES HAGENBACH.

⁂ A letter in the *Journal* of October 7 (p. 836) describes the use of antihistaminics in treating nocturnal frequency.—ED., *B.M.J.*

Sea-sickness

SIR,—In the correspondence (see, for instance, November 11, p. 1117) following Professor Burn's article (*Journal*, September 23, p. 691) no reference appears to have been made to the use of "benzedrine" (amphetamine sulphate) as a cure for travel-sickness. In 1949 I was told of this action of the drug by a colleague in the Colonial Medical Service. Since then I have tried it on myself and have given it to other sufferers with (so far as I was able to judge) excellent results.

The dosage is one-half to one tablet (2.5–5 mg.), given after the person has started to feel ill. It is not necessary to use the drug prophylactically, since it appears to work so well as a "corpse-reviver." In fact I withheld the drug deliberately in many instances because I wished to be quite sure that (*a*) the person concerned really was going to develop sea-sickness, and (*b*) the benzedrine was not merely acting as a placebo.

Benzedrine has none of the disadvantages of the hyoscine preparations, the soporific effect of which is shared by the antihistamine group. It does, of course, tend to interfere with sleep, but this effect can be countered by a barbiturate.

As I have never had the opportunity of carrying out a properly controlled trial of the drug it should be noted that the foregoing is only a personal impression. It would, however, be interesting to hear other people's experiences with the use of benzedrine for this purpose.—I am, etc.,

ALAN ROBINSON,
Lee-on-Solent. Surgeon Lieutenant-Commander, R.N.

SIR,—The recent correspondence (October 21, p. 946; November 11, p. 1117) has prompted me to write a few facts noted during my two years' experience as a senior medical officer in troop transports (1945–7). As my duties were often combined with those of ship surgeon my patients included both sexes and many nationalities. There appeared to be three types of sea-sickness: (1) Actual vomiting, which was the most common type and was occasionally accompanied by haematemesis. (2) Sudden loss of consciousness with cold, clammy sweating, rapid thready pulse, and marked fall in blood pressure. (3) Severe intractable headache, unrelieved by the more common analgesics, which always cleared up on disembarkation. In these cases there was no apparent organic cause or anxiety state. It was infrequent, in my experience, for children under the age of 7 years to be sea-sick.

As regards treatment for adults, I found a combination of 1 gr. (65 mg.) phenobarbitone and hyoscine hydrobromide 1/100 gr. (0.65 mg.) most effective in the large majority of cases under even the most adverse conditions. This could be repeated six-hourly if necessary, to a total of 3 gr. (195 mg.) phenobarbitone and 3/100 gr. (1.95 mg.) hyoscine hydrobromide in 24 hours.

For children aged 10 to 14 years (provided they were of reasonable physique) I prescribed 1/200–1/100 gr. hyoscine hydrobromide with good effect.

Naturally in some cases during treatment there was some drowsiness, but I found the large majority of sufferers preferred drowsiness to sickness. In several instances (expectant mothers, cardiac cases, acute anxiety states, etc.) where there had been persistent vomiting and where there was no hope of reaching land within three to four days I was forced to give a hypodermic injection of 1/3 gr. (22 mg.) "omnopon" with 1/150 gr. scopolamine. Rectal administration of drugs proved impracticable for various reasons. Other remedies, bromides, chloretone, phenobarbitone by itself, and even champagne, were of little use.

I had no experience of amphetamine, and of course at that time the various antihistamine drugs were not available.—I am, etc.,

Oxshott, Surrey. J. D. M. LYTLE.

Nail-plate for Intertrochanteric Fractures

SIR,—Few orthopaedic surgeons to-day would disagree with Messrs. G. P. Arden and G. J. Walley for their advocacy (*Journal*, November 11, p. 1094) of the nail-plate as the ideal form of treatment of the intertrochanteric fracture of the femur. But as a result of their experience they conclude that certain modifications of their method are necessary:

"More blood transfusion at operation, to control shock." If the patient is anaemic before the operation I would agree, but otherwise it is unnecessary. When a postero-lateral incision is employed haemorrhage is negligible and the operation upsets the patient no more than the ordinary pinning operation for subcapital fractures.

"Modification of the nail-plate." (Four fins, to prevent bending of the nail; a single Egger-type slot in the plate, to encourage early union; a serrated spring compression washer or lock-nut, to prevent the nut becoming loose, and thus prevent a varus deformity.)

The first and last of these are necessary because of the defects in the type of nail used (McKee plate, 35 cases; McLaughlin plate, two cases). I suggest that a change-over to the Capener-Neufeld plate will obviate further trouble. The latter V type of nail rarely bends unless poorly tempered, and it has no nuts to work loose.

I entirely fail to see the value of the Egger slot in the plate to encourage early union. I cannot recall a case of delayed or non-united intertrochanteric fracture. The nail does not obtain a rigid grip in the neck of the femur. Impaction of the fragments occurs as a result of muscle pull or weight-bearing, which cause the nail to slide further inwards. For this reason a long nail should not be used (3¼ in. (8.3 cm.) is about the average length), otherwise the slight impaction that frequently occurs will cause the nail to penetrate the cartilage of the head of the femur.

—I am, etc.,

Exeter. F. C. DURBIN.

SIR,—I published a small series of cases (17 consecutive cases in six months) of intertrochanteric fractures of the femur in the *Lancet* in January, 1944, describing the use of a trifin nail and plate in the treatment of these fractures. Since then I have done over 150 cases, and I should like to confirm all the advantages claimed by Mr. G. P. Arden and Mr. G. J. Walley (November 11, p. 1094). I have also experienced the same complications, and have adopted almost the same measures to avoid them.

Penetration of the Head of the Femur by the Nail.—This complication is particularly liable to occur when a plate is used in connexion with a nail, the plate preventing the nail from coming out when absorption takes place at the fracture site, the result being that the nail tends to travel farther into the head. My technique to stop this consists in allowing at least ½ in. (1.3 cm.) clear between the upper end of the nail and the outline of the femoral head, but before this final position is obtained I release all traction on the limb and impact the fragments, so that there is no gap between them to start with.

Bending of the Nail.—The nail can be made stronger either by having a four-flanged nail as suggested in the recent article in the *British Medical Journal*, or by having it made of stouter steel. I have not met with much success in trying to develop a nail of tougher material, and it is obviously not desirable to have a nail of too great a cross-sectional area. There are, however, some modifications in technique which lessen the strain on the nail. First of all, the nail should be placed as vertically as possible. Secondly, if the fracture is low so that the nail simply holds the upper fragment and the plate holds the lower one, then the use of slots instead of holes in the plate will allow subsequent taking-up at the fracture site, so that the fragments remain in contact and no gap

will occur. Thirdly, the release of distraction and firm impaction as a final procedure gives initial consolidation of the fracture and considerably diminishes subsequent strain on the nail.

Since using these measures I seldom see any bending of the nail, so I can vouch for their effectiveness in practice.

Bending of the Neck of the Blade-plate.—The neck of the plate is its weakest part and was particularly liable to bend, but it has been considerably strengthened in later models, so much so that it is advisable to use a vice to hold the plate in order to adjust the angle to the exact requirements before it is inserted.

Loosening of the Nuts.—This complication did occur in my early cases when I used a screw, but since then I have been using a special type of self-locking nut made for me by Mr. Drew, of Down Bros. The nut is firmly tightened by a stout box spanner, and I have not seen one come loose for several years.

Using these modifications, my impression is that a more accurate reduction can be maintained. The operative mortality and the immediate post-operative mortality have become almost negligible since a light unilateral spinal anaesthetic of "nupercaine" has been used.

Finally, I should like to mention that I have used stainless steel plates with vitallium screws for the last five years and I have not been troubled by any electrolytic reaction. In fact, in the few cases where I have removed the apparatus several years after its insertion there has been less reaction than when stainless steel screws and a stainless steel plate were used.—I am, etc.,

Norwich. G. K. McKEE.

Proper Use of Anticoagulants

SIR,—Drs. J. A. Tulloch and A. Rae Gilchrist in their excellent article (October 28, p. 965) give heparin by interrupted intravenous injections at intervals of eight hours in most of their cases. They assess adequacy of dosage by estimation of clotting time one hour after the injection. As the clotting time would be practically normal in three to four hours, this method affords no protection against a further thrombosis in the four hours preceding the next injection. This is more than a theoretical consideration and may account for at least some of those cases in which further thrombo-embolic phenomena occurred.

Drs. Tulloch and Gilchrist state that they have been disappointed with depot-heparin and heparin-retard, partly on account of the intense and persistent local pain after the intramuscular injection and partly on account of irregular absorption, but have found "Heparin-Evans" to be more satisfactory. Nevertheless, I believe that intravenous heparin will always be preferable to intramuscular heparin, because in the case of the latter the rate of the absorption will always vary to some degree and the clotting time at any given moment will, therefore, be unpredictable. Moreover, the heparin effect can never be wholly neutralized by protamine sulphate, which will instantaneously flocculate the whole of an intravenous dose.

There are several simple and efficient methods of administering heparin intravenously without the necessity of employing a continuous drip, with its many disadvantages, or of subjecting an ill patient to the discomfort of repeated injections through the skin. Perhaps the most popular is the use of the Gordh's needle, but, if the administration of heparin is to be continued for longer than 24 hours, polythene tubing can be inserted into one of the antecubital veins through a wide-bore transfusion needle. The latter is then withdrawn and a Gordh's needle fixed tightly into the free end of the polythene tubing. If such a needle is unavailable a satisfactory substitute can be easily improvised by fitting about 1½ in. (3.7 cm.) of rubber tubing from a blood transfusion set to an ordinary hypodermic needle. When communication has been established with a vein, either directly or through polythene tubing, the distal end of the rubber tubing is closed by a clip; injections can then be made directly into the rubber tubing, which seals automatically when the needle is withdrawn.

As a general rule 5,000 units of heparin at 3-hourly intervals, or 10,000 units at 4-hourly intervals, will be found to suffice. The dosage, however, may have to be increased or diminished depending on the length of the clotting time, which is taken three or four hours after the second injection, corresponding to the interval chosen. A much larger initial dose may be administered, and, in addition, allowance must be made for the volume of dead space in the apparatus used.

Now that "tromexan" is generally available there is no possible justification for the use of "dicoumarol." The action of tromexan is more easily controllable, and if an overdose should be given the patient is in danger for only a matter of hours. As Drs. Tulloch and Gilchrist advocate, tromexan should be given in small divided doses throughout the day. Unfortunately the smallest tablet manufactured is 100 mg., and this is not easy to split up. As some patients require a maintenance dose of as little as 150 mg. daily it would be convenient if smaller 50 mg. sugar-coated tablets were put on the market. Also there are patients who require very much larger daily maintenance doses; for example, in one of my cases I had to give 1,200 mg. daily in order to produce a satisfactory rise in prothrombin time.

Because of this wide variation in individual requirements I would like to conclude by reiterating Drs. Tulloch and Gilchrist's warning of the importance of a careful and efficient technique for the estimation of prothrombin times.—I am, etc.,

London, W.6 C. HOUGIE.

Diagnosis of Placenta Praevia

SIR,—In the report on the discussion on the diagnosis and treatment of placenta praevia at the Royal Society of Medicine (November 4, p. 1055) I was surprised to read of the emphasis placed on abstinence from vaginal examination in the diagnosis of this condition. How can the certain diagnosis of placenta praevia be made without the insertion of a finger through the os? From the history of the case one suspects the presence of praevia, and by abdominal palpation one can diagnose the presence of a low-lying placenta—but surely this is quite a different thing from diagnosing placenta praevia of such a degree as to necessitate the performance of a caesarean section. Even in the few cases in which a vaginal examination appears superfluous, the insertion of a finger through the cervix may well disprove an apparently certain diagnosis. The following case is an example.

On the evening of October 8 I was called to see a woman aged 30 who was in the 37th week of her fourth pregnancy. While rising from the bridge-table she had suffered a sudden painless haemorrhage, sufficient in amount to cause a trail of blood spots across the floor and a sizeable pool on the lavatory floor. I estimated the blood loss at 10–15 oz. (300–450 ml.). On examination, the general condition was good, there were no signs of toxaemia, the uterus was of normal consistency, the presentation was vertex, and the foetal head was freely mobile. Even gentle palpation of the abdomen caused an increase of the slight trickle of vaginal bleeding which had persisted. A provisional diagnosis of central or marginal placenta praevia was made and the patient transferred to hospital. The blood group was determined, compatible blood made available, and the patient taken to theatre prepared for caesarean section. Under anaesthesia, a vaginal examination was performed. Gentle palpation through the fornices revealed the head to be easily felt, and did not occasion any gross bleeding. A finger was then inserted through the os and the lower segment explored. No placental tissue could be felt over the os or within 1 or 2 in. (2.5 or 5 cm.) of it. There was no further bleeding. The membranes were ruptured, using Kocher's forceps, the head was pushed into the pelvis, and a binder applied. Contractions commenced three hours later, and after a short labour lasting four and a half hours a live child weighing 6 lb. 1 oz. (2.7 kg.) was delivered. Following the birth of the placenta, the uterus did not contract well and a sharp post-partum haemorrhage of over 20 oz. (600 ml.) occurred, necessitating a blood transfusion.

The puerperium was uneventful. Examination of the placenta and membranes was inconclusive, and no certain cause for the antepartum haemorrhage was found, although one presumes that it was due to a lateral placenta praevia.

I feel that greater emphasis should be given to Professor Browne's statement that the largest group of cases of antepartum haemorrhage are those in which the cause is not known. If this is kept in mind, fewer series of cases showing a caesarean section rate of 70% will be produced. In my view, a careful vaginal examination performed in the theatre with all the preparations made for operation and compatible blood at hand cannot increase the risk to the patient. No matter how skilled the surgeon, the operation of caesarean section does carry a mortality rate, and it is only justified if the condition for which it is performed has first been diagnosed with certainty.—I am, etc.,

Taunton, Somerset. J. M. THOMSON.

The Clinician and Cancer Records

SIR,—In *The Times* of November 2 a leading article was devoted to cancer records (see also *Journal*, November 4, p. 1046), and it was mentioned that such records on a national scale were started by the Radium Commission. As one of those members of the Commission who helped in that work, and who has been interested in cancer records for many years, I would like to point out that the real difficulties with which hospital record departments have to contend are the clinician's notes. A busy clinician is inclined to jot down such notes as he thinks will be useful to him when he sees the patient again a few weeks later while the treatment and other points are still fresh in his mind. He forgets that an analysis has to be made from his notes five years later and that this is the foundation on which the interim report just published by Dr. Percy Stocks depends. Something must be done to improve the clinician's notes, preferably by having printed headings, if the final reports are to be accurate and worth compiling.—I am, etc.,

London, W.1. MALCOLM DONALDSON.

An Author Defends His Book

SIR,—May I be allowed to comment on the review (November 11, p. 1100) by Sir Stewart Duke-Elder of my book? The principles this work sets out to establish are those of general physiology applied to the eye, so that the conditions governing its component tissues differ in no way from those which obtain elsewhere for similar tissues and analogous situations.

This conception of physiological harmony and conformity is apparently distasteful to Sir Stewart, for he says, "The sections on physiology should be read critically, for seldom will there be found so many sweeping conclusions based on premises so slender and sometimes of questionable validity." In the light of such criticism I draw attention to the mechanism of accommodation. According to established convention the vascular choroid functions as counterweight to the lens, and the unstriated ciliary muscle is actuated by a single nerve. These two tissues are in consequence unique, not merely in mammalia but in the whole range of the animal kingdom. Nowhere else can a vascular structure be found subjected to constant stress, or unstriated muscle actuated except by two nerves and functioning accordingly. To dispense with such anomalies and substitute a mechanism in accord with physiological, anatomical, and mechanical principles is the solution.—I am, etc.,

Nottingham. THOMSON HENDERSON.

POINTS FROM LETTERS

Syphilis and "Chloromycetin"

Dr. NORMAN MELLOR (Cereal, Alberta) writes: I was interested to read Professor L. P. Garrod's article in the Refresher Course (September 23, p. 722) regarding the activity of "chloromycetin" and "aureomycin," and would like to draw his attention to the makers' claim for the former drug in the treatment of syphilis. . . . Messrs. Parke, Davis and Co. state that "chloromycetin offers considerable promise as a means of treating those individuals with syphilis in whom more established therapeutic measures are not applicable." This statement is made after citing investigations by sundry workers (*Sth. med. J. Bgham, Ala*, 1949, **42**, 988; *Science*, 1949, **110**, 639; *Amer. J. Syph.*, 1949, **33**, 509; *S. Afr. med. J.*, 1949, **23**, 1043) who, while admitting that the drug has a low antitreponemal action *in vitro*, claim that remarkable healing of the primary lesion occurs in a very short time. This would appear to be a direct contradiction of Professor Garrod's statement that the drug has no useful action on *T. pallidum* and that it is incapable of masking syphilis. Surely, if a drug is effective in healing the primary lesion, therein lies its danger should its therapeutic value be limited to this stage of the disease.

Eccentric Nozzles for Syringes

Dr. J. P. ANDERSON (Stockton-on-Tees) writes: Can the manufacturers of syringes give any reasons why syringes are still made with concentric rather than eccentric nozzles? Surely there are no disadvantages likely to be encountered if *all* nozzles are eccentric. The reason for this question is, of course, the important fact that all syringes are probably used (from necessity) at some time for intravenous work. A concentric nozzle is a great handicap in any syringe above the 2 ml. size, and becomes increasingly so as the size increases.

Obituary

NEIL F. SINCLAIR, F.R.C.S.

Mr. Neil Sinclair, who was a well-known surgeon on the staff of several hospitals in and around London, died at his home in London on November 14 at the age of 65.

Neil Frederick Sinclair was born in Jamaica, the son of a leading medical practitioner, being the eldest of six children. After receiving his early education on the island, he came to England at the age of 16 and began his medical studies at the London Hospital in 1903. After a successful career as a student—he gained the Anderson and Dressers' prizes—he qualified in 1908. For several years thereafter he devoted his time to the principal resident appointments at the London Hospital. He was house-surgeon to the late Sir Frederick Eve and to Mr. Furnivall, and in 1911 was president of the residents' mess when holding the post of senior resident accoucheur. He served in the first world war as a captain in the R.A.M.C., and many of his old friends will remember him during this period by the affectionate name of "Bulgie." He took the F.R.C.S.Ed. diploma in 1916 and subsequently became surgical registrar at the West London Hospital. After becoming a Fellow of the Royal College of Surgeons of England in 1920 he was appointed to the staff of the West London Hospital as an assistant surgeon. In 1930 he became a full surgeon to this hospital, and in 1936, on the death of Mr. Tyrrell Grey, he became its senior surgeon. He played an active part in the postgraduate teaching at the West London Hospital and for a time was the dean of its postgraduate school. He was a member of the surgical staff of a number of other hospitals and continued as senior surgeon on the staff of King George Hospital, Ilford, and the Northwood District Hospital to the time of his death.

Sinclair took a special interest in the work of the West London Medico-Chirurgical Society and held the post of secretary and later of president of this society. He was also a very keen member and a past secretary of the Medical Society of London. He completed a full term as a member of the court of examiners of the Royal College of Surgeons of England and became known as a very fair and wise examiner. His publications were concerned chiefly with abdominal surgery, and he gained a considerable reputation as an abdominal surgeon. He was also particularly interested in the surgery of the thyroid gland.

Mr. A. M. A. Moore writes: Mr. Neil Sinclair possessed sound surgical judgment and great technical skill, and his very many friends will remember the pleasure of seeing him at work in the operating theatre. He became a great personal friend of many of his patients and never at any time failed to appreciate all their human problems. Many of England's younger surgeons owe much to the interest and drive of this remarkable man, and the country is all the poorer by his passing. His memory will always be cherished in the hospitals in which he worked and in the hearts of his host of friends. He leaves a widow, a daughter, and a son, who is at the moment a student at his father's old medical school. The deepest sympathy is extended to them in their bereavement.

Mr. G. P. Grant Batchelor writes: Neil Sinclair was outstanding. Under a modest exterior lay a keen intelligence backed by decisiveness of character yet tempered by kindliness and human understanding. Although the

best that was in him was devoted to surgery, his active mind probed into a wide diversity of subjects from religion and architecture to fishing and philately. He enjoyed discussion and argument—a pastime in which his natural friendliness and approachability enabled him to indulge freely. He entered the lists of surgery while in the R.A.M.C. in the first world war and savoured to the full the grim fruits of trench warfare. This marks him as belonging to the era of general surgeons which preceded the more restricted specialization of to-day. Whatever he did he did extremely well, and few excelled the neatness, steadiness, and precision of his technique. On the academic side he wrote comparatively little, but more than made up for this by the breadth of his devotion to teaching and the very active support he gave over the years to many learned societies. As dean of the Postgraduate College at the West London, before postgraduate gave way to undergraduate teaching in the middle 'thirties, and thereafter as lecturer in surgery, many a student must remember him with gratitude for his kindly help and interest. Neil Sinclair practised surgery in many hospitals, but the West London claimed first place in his affection, and the standing and prestige which the hospital enjoys to-day bears his stamp upon it. Up to within a few days of his death he was working and teaching there. His host of friends and colleagues will long cherish the memory of his kindliness, his friendliness, his ability, and, not least, his courage and stoicism in his last illness.

P. H. P. writes: As an old student of the West London Hospital I should like to add a tribute to the memory of Neil Sinclair. He was, of course, a brilliant surgeon, and he could make the most difficult operation appear simple by the calm smoothness of his technique. He once said he planned his operations to avoid any unnecessary movement, and, indeed, he achieved this end. He had the ideal temperament for a surgeon—a calm confidence, imperturbability, and deep humility. To his work he brought a wide understanding of human nature, and by his kindly manner gained the confidence of all his patients, rich and poor. His passing leaves a gap which none can fill.

HELEN M. SEXTON, M.B.

Dr. Helen Mary Sexton died in London on October 10, in her 89th year. She was born in this country, but went to Australia as a tiny child, where her father, an architect, died as a young man. After the death of her mother (who opposed any idea of medical training) Helen Sexton became one of the first women students at Melbourne University and graduated M.B., B.S. in 1892 at the age of 30. Within a short time she was elected as the only woman on the staff of 12 at the Gynaecological Hospital, Melbourne, where appointment was by vote of the subscribers. She retired through ill-health in 1912, after founding the Victoria Hospital for Women (now 600 beds) with five other medical women. Soon after the outbreak of the first world war Dr. Sexton took a small field hospital to France, the gift of herself and other women doctors. She served with the French with the rank of *majeur*, and when the hospital was disbanded she was given a temporary appointment at the great Val de Grâce in Paris. In 1917 she finally retired and afterwards spent many years in satisfying her delight in travel and in European art, making her home in Italy for 10 years. During the last decade of her life she was almost totally helpless, though her splendid smile still shone, and the few words that she could speak were always concerned with somebody's well-being. Both in Australia and in this country her colleagues held her in high esteem.—A. G.

J. H. ANDERSON, C.M.G., C.B.E., M.D., F.R.A.C.P.

Professor Richard J. A. Berry writes: It is with more than ordinary regret that I have just read of the death of Dr. J. H. Anderson (whose obituary notice appeared in last week's *Journal*), much better known to me as "Jock"; and who of his contemporaries and friends knew him by any other name? He was known to me personally and professionally for the whole of his medical lifetime, and there are few men for whom I had a greater personal esteem or in whom I consistently reposed a greater trust, for I knew he was worthy. It was in Anderson's senior year, as a student of anatomy in the University of Melbourne, that he first came under my notice, and from that time our lifelong friendship dates. He and his fellow students—such men as the late Alan Newton, Victor Hurley, Bill Upjohn, Ike Jones, to mention only a few and to give them not their well-earned more dignified professional titles but those by which they were affectionately known, unknown to themselves, by their professors and teachers, of whom I was fortunate to be one—these were the men who so largely helped in building up the Melbourne Medical School and in raising it from what it was in Anderson's third year to what it has since become. And what it is only those who have seen it can realize. In this pioneer work Anderson was pre-eminent, and I at least shall not readily forget it, nor, I think, will many others.

Dr. JOHN THOMSON MCLACHLAN died on October 26 in Glasgow. Born in the Vale of Leven, he was educated at Dumbarton Academy and Glasgow University, where he studied medicine. He graduated M.B., C.M. in 1888, and proceeded M.D. in 1896. He had a varied career as a general practitioner. After working for two years as assistant medical officer in an asylum in Lanarkshire, he went into practice in Dornoch, Sutherlandshire. After some years he moved to Glasgow, and among other appointments he held that of surgeon to the central police district. He gave up general practice when 70 years of age, and then worked as a locumtenent, chiefly in mental hospitals. McLachlan's main interest in life was medicine, and he wrote easily about all aspects of it. Numerous letters of his appeared in this *Journal*; his last, written a few months ago, was on the subject of medical education. He was twice married, and leaves no family.—J. H.

Dr. THOMAS ALFRED MAYO, who practised in Cowes for 37 years, died at his home in Cowes on November 1, aged 75 years. A native of Mildenhall, Suffolk, he was educated at Epsom College, Clare College, Cambridge—to which he won a senior scholarship and where he gained a first in the natural sciences tripos—and St. Bartholomew's Hospital. He qualified in 1898, graduating M.B. a year later. In 1900 he became a Fellow of the Royal College of Surgeons. Mayo went to Cowes in 1902 and became a partner of Drs. William and Edgar Hoffmeister. He was later in partnership with Dr. S. Hartill, of East Cowes, and lastly with Dr. G. M. Balfour. During the time he practised in Cowes he was a member of the honorary medical staff of the Frank James Cottage Hospital, and was afterwards consultant surgeon to the same hospital and also to the Kind Edward VII Convalescent Home at Osborne. For some years he was medical officer of health and police surgeon for Cowes. During the first world war he served with the R.A.M.C., chiefly in Malta, and during the last war was one of the examining doctors on the local medical board. He was chairman of the I.W. Local Medical War Committee and continued in this position until his death. Over a long period he was actively connected with the work of the British Red Cross Society. In 1938–9 he was chairman of the Isle of Wight Division of the B.M.A. He retired in 1939, after 37 years of devoted service to the community, during which time he won the respect and gratitude of his patients by his reassuring manner and kindliness of heart. His colleagues mourn the

passing of a leader in our profession whose kindness and consideration to junior medical men were outstanding. He leaves a widow and a married daughter, to whom sincere sympathy is extended.—H. S. H. W.

Medical Notes in Parliament

Compulsory Trade Union Membership for Doctors

Dr. CHARLES HILL on November 15 drew attention to the action of Durham County Council in passing on November 1 a resolution requiring every member of its staff at all levels to produce evidence of trade union membership, under threat of dismissal. He added that the requirement was not to belong to a particular trade union and that in the case at least of doctors it was interpreted as one to belong to their professional association, if they preferred that to belonging to a union. It seemed to him that this was wrong in three or four respects. To secure members under duress was to damage the organization which secured them. A body from which a member who was dissatisfied with its officers, its policy, or its work could not voluntarily resign without losing his job was an unhealthy one. The role of the local authority was to employ the best-qualified persons to do its work, whether they belonged to this or that organization or not. It was utterly wrong for a man's job to be at the mercy not only of the employing authority but also of the trade union to which he belonged. For the loss of membership for some offence within the trade union organization to involve the loss of a man's job was utterly wrong.

Mrs. JEAN MANN asked whether that argument applied to the British Medical Association and the doctors.

Dr. HILL replied that the British Medical Association was a voluntary body. The Durham County Council had ordered the doctors to join the trade union or the British Medical Association as they chose, but the attitude of the British Medical Association was that no doctor should be required to join any body, not even the B.M.A.

Mrs. MANN asked whether Dr. Hill knew of any doctors who had dared not to join the B.M.A.

Dr. HILL replied that the membership of the British Medical Association was between 75% and 80% of the profession, and there was no compulsion on any man to join that body. He sometimes thought that the nation was losing its capacity for anger at such interference with the freedom of the individual. The battle for the right of association had been magnificent and necessary. As one who had spent many years in collective bargaining he desired men and women to belong to their appropriate trade unions and professional associations. It seemed to him utterly wrong that a local authority should adopt the attitude of the Durham County Council. The issue had not been raised prominently since 1946, which was the time of the Willesden incident. The Minister had taken action in that case which Dr. Hill hoped he would take in this one (see *British Medical Journal*, 1946, **2**, 924).

Dr. H. B. W. MORGAN said the local authority asked its employees to belong to some representative organization with which the authority could negotiate regarding remuneration or conditions of work. It did not ask the doctors to join the B.M.A. They could join the Medical Practitioners Union, which was registered as a trade union and affiliated to the T.U.C., which the B.M.A. was not. It was reasonable when trade unionism was so widely recognized that an organization should say, "We think you should for our convenience, and for your own, join one organization, and we demand that as a condition of employment." The point was the convenience of the negotiating body, which was spending public money or money granted by Parliament.

Dr. HILL pointed out that the Whitley structure for negotiation existed.

Dr. MORGAN said that freedom of the individual had nothing to do with the matter. If individuals need not belong to a recognized body, what was the Durham County Council to do? Was it to negotiate with the trade unions and leave isolated individuals outside to get the advantages of negotiation by the trade unions? That was not right.

Mr. E. R. BOWEN said the Minister of Labour had expressed views diametrically opposed to everything that had been said by Dr. Morgan. In December, 1946, he had said that compulsion by employers to join trade unions was likely to be detrimental to harmonious industrial relations. Over half the working population of the country consisted of people who were not members of trade unions affiliated to the T.U.C. That indicated the range of people who might be affected by the action of the Durham County Council. People had been employed by the Durham County Council for 20 or 30 years. Were they now to be told that a new condition of employment had been introduced, and that unless they were prepared to conform with that condition they were to be sacked?

Mr. GORDON LANG said he found himself in agreement with Dr. Hill. If it was to become a feature of public administrative life that a local governing body could order people to join a trade union he could conceive of occasions when there might be an instruction that no employees of certain bodies were to belong to any trade union. It was not the duty of a local body to impose its will in that way upon its employees. Liberty was dwindling in this land and he regretted it.

Mr. C. H. GAGE said it was for the trade unions themselves to realize that the days of these restrictive practices were over.

Mr. FRED MESSER said that trade unionism as a condition of employment had been in operation for many years. In many industries a man must show before he could start work that he was a member of his trade union. The Durham County Council had been democratically elected. It had not done anything which was against the law. It would be very dangerous if instructions were to come from Whitehall to local authorities who believed that, being elected by the people, they had a right to speak in the name of the people.

Sir RICHARD ACLAND said the trade unions ought to respect the genuine feelings of large numbers of people and not seem to seek greater power over individuals.

Mr. A. BLENKINSOP replied for the Ministry of Health. He said that the circular issued by the Ministry to local authorities on December 6, 1946, was still the view of the department and of the Government on this question. The Ministry regretted the resolution passed by the Durham County Council. At the same time it was anxious that employees of local authorities as well as other workers in regular employment should join their respective trade union or professional body and should be at liberty to do so. In January, 1948, Mr. Bevan in reply to a question had said that he hoped that persons employed in the National Health Service would be encouraged to belong to their appropriate organizations, but it would not be a condition of employment and there would be no pressure on anyone to belong to any organization, whether professional or trade union. That view had also been expressed by the Minister of Labour.

The House should remember that the Ministry was concerned merely with advising local authorities on matters of this kind, but it would take measures to ensure that the attention of the Durham County Council was drawn to the circular issued in 1946 and to the reply of Mr. Isaacs in 1948.

Dr. HILL asked whether this action would be taken with the least possible delay, because Wednesday, November 22, was the date by which proof of trade union membership had to be given.

Mr. BLENKINSOP said the only attitude which the Ministry could take up was one of adviser to the authority on this point. The Ministry appreciated the point made by Mr. Messer that the county council was the locally elected authority and had full power in this matter.

Sir HUGH LUCAS-TOOTH asked that the advice given by the department should be in the strongest possible terms, and Mr. BLENKINSOP made it clear that the action taken was deplored by his Minister.

The Trade Union Bill, "to prohibit local and other public authorities from making membership or non-membership of a trade union a condition of employment or of continuance in employment," was presented on November 17 by Mr. Nigel Davies, who had been successful in the ballot for private members' Bills. Its second reading was set down for April 6.

Medicine in the Colonies

In the debate on November 9 on the second reading of the Colonial Development and Welfare Bill Mr. EDWARD DAVIES said that the worst obstacle to health in the Colonies was undernourishment: the people had not the energy to produce more foods or goods.

Mr. S. S. AWBERY said the need for welfare schemes in Nigeria was shown by the fact that it had one doctor for every 133,000 people. It had one hospital bed for every 3,700 people, as against 1 for every 250 in the United Kingdom. Nigeria had 10 dentists for 23 million people. Its infant mortality was 110 per 1,000 and T.B. was the cause of 10% of the deaths.

Mr. G. H. C. BING said that when medical skill fell behind engineering ability a series of terrible tragedies resulted. Ceylon had been able to maintain a population of 20 million by an irrigation system of dams: those dams did not breed malaria owing to the irrigation level being continually altered. War came, the levels remained the same, mosquitoes bred, and in a generation the population of Ceylon fell from 20 million to less than 2 million people. We now knew how to control malaria, but were likely to find difficulties from it when we came to deal with those wholesale schemes for irrigation which were essential in Africa. In Africa at the moment malaria was endemic and the people needed a sufficient level of education for them to take some anti-malaria drug such as paludrine or mepacrine. Two other great difficulties would have to be faced in any system of irrigation for development of African agriculture. The first was the presence of bilharzia and tsetse-borne diseases, sleeping sickness, and the nagana disease which affected cattle. The Egyptian Government had been encouraged in the disastrous course of substituting irrigation from dams for the Nile floods. Previously there had been an incidence of bilharzia in some villages as low as 2%, but there was now an incidence of something like 75%. The elimination of the tsetse fly was a problem not only of medicine but of town planning and administration and engineering. Antrycide had not turned out to be anything like the short cut to the elimination of the fly that people had first thought. Even if it had been as good as was hoped they would still have had to train African personnel in the veterinary services and face a considerable amount of expenditure.

Mr. L. D. GAMMANS said that in West Africa there were nearly a thousand posts, normally filled from the United Kingdom, for which applicants could not be found.

Mr. DOUGLAS HOUGHTON referred to a report, *Development and Welfare in the West Indies*, which had drawn attention to the excessive rate of population growth. It estimated that the population would increase by 45% in 25 years. The rapid growth of the child population imposed a great strain on the health visitors and health services. The mortality rate had practically halved in the last 50 years, but the birth rate was still very high throughout all the Colonies in the West Indies, and if there was no enlightenment on family limitation then family increase would replace some tropical diseases by diseases of malnutrition and poverty. The West Indies Royal Commission of 1938–9 had recommended public enlightenment on birth control. Why did the medical services of Jamaica discourage the use of contraceptive devices? The only birth control clinic in Kingston, Jamaica, was a voluntary one and was in serious difficulties from lack of support.

Dr. H. B. W. MORGAN said that if the Government wished to fail at the next election they had only to include birth control in any welfare scheme.

Mr. E. B. WAKEFIELD said the problem was not simple. In India plague, cholera, and dysentery had been controlled by the devoted work of doctors; and by the development of roads and railways plague and famine were countered. Now the population had grown so rapidly that all Britain had succeeded in doing was to lower the average standard of life. It was wrong to suppose that by pouring money into the Colonies they would raise the standard of living. Those who had been in Johannesburg knew the appalling conditions of labour in that city. He himself had seen appalling results in Arabia, where oil had been discovered and gold poured in.

Private Patients in Hospital

Captain M. BULLOCK on November 9 asked Mr. Bevan to consider allowing patients who occupy private wards, if they so desired, to have deducted from the charges made for such private wards the amount which would be chargeable to public funds if they were to receive treatment in a public ward. He further asked whether the Minister was aware of the different amounts charged by each hospital in the country for treatment in their private wards, and whether there was any possibility of the charge being made more uniform.

Mr. BEVAN answered that under the National Health Service Act, 1946, the charge for a private bed at any hospital must be such as to cover the whole cost of the accommodation and services provided for the patient at that hospital. He had no power to remit any part of this cost or to introduce uniform charges at hospitals.

Payment in Maternity Cases

The Hon. Mr. M. L. ASTOR on November 9 asked Mr. Bevan to make arrangements whereby in maternity cases, when either the matron of a hospital or a patient's doctor certified that the birth was imminent but no bed was available under the National Health Service, the patient could be reimbursed for expenses incurred in obtaining medical care privately.

Mr. BEVAN replied that the primary use of hospital maternity beds must be for mothers needing institutional confinement. The domiciliary maternity services were available without charge to the remainder. He had no power to make payments in the manner suggested.

Compensation for Doctors

Mr. H. CHANNON asked on November 9 at what date Mr. Bevan proposed to apportion the £66m. among doctors on their retirement in compensation for the goodwill of their practices.

Mr. ANEURIN BEVAN said that apportionment would not be possible until the claims of all doctors had been received and assessed. The final date for the submission of claims had been extended to December 31, 1950, or, in special circumstances, February 28, 1951.

Mr. CHANNON said many doctors had waited over two years and perhaps suffered hardship.

Mr. BEVAN said these cases were always met by making a grant of a substantial portion of the sum needed.

Mr. E. FERNYHOUGH asked whether any doctor who left the Health Service had a claim on this £66m.

Mr. BEVAN replied that he certainly had.

Free Treatment when Abroad

Asked by Colonel E. R. G. HEATH on November 9 whether British citizens when abroad could receive Health Service benefits without payment, Mr. BEVAN stated that arrangements for varying degrees of reciprocity had been or were being made with the Isle of Man, the States of Jersey and Guernsey, Belgium, France, Luxembourg, and the Netherlands.

Colonel HEATH pointed out that many merchant seamen paid contributions but for nine months in the year could not get benefits.

Mr. BEVAN said the Government was trying to arrange reciprocity, but other countries had not our facilities.

Colonel HEATH also asked the Minister of Health to make regulations so that foreign residents visiting this country would have to pay a charge for using the Health Service.

Mr. BEVAN said he was keeping this under review, but was not at present satisfied that there was enough evidence of abuses to justify action, since the expense of administration would be far more than the gain to the Health Service.

The fourth Annual Congress of the International Scientific Film Association was held at Florence on October 14–22, Britain being represented by a delegation of 10 members. It was decided to set up in Brussels an international reference film library of scientific films, and a standard system of recording was adopted.

Universities and Colleges

UNIVERSITY OF OXFORD

On November 18 the honorary degree of D.Sc. was conferred on Dr. Oscar Vogt, director of the Berlin Institute for Brain Research.

UNIVERSITY OF CAMBRIDGE

In Congregation on November 11 the following degrees were conferred:

PH.D.—*Mary E. P. Hele, M.B., B.Chir., Joan E. Keilin.
M.B.—S. E. Birdsall.

*By proxy.

UNIVERSITY OF WALES

The following candidates at the Welsh National School of Medicine have satisfied the examiners at the examination indicated:

TUBERCULOUS DISEASES DIPLOMA.—K. Chandar, P. J. Galvin, Marjorie S. Oxley.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH

At the annual meeting of the College held on October 25 the following were elected to the Council of the College: Professor R. C. Alexander, Mr. K. Paterson Brown, Mr. John Bruce, Mr. Arthur J. C. Hamilton, Professor C. F. W. Illingworth, Mr. James S. Jeffrey, Sir James R. Learmonth, Mr. Robert Mailer, Professor Walter Mercer, Mr. T. McWalter Millar, Mr. Douglas Miller, and Mr. R. Leslie Stewart.

The names of the officers of the College elected for the ensuing year were published in the *Journal* of November 11 (p. 1123).

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW

Professor Ian Aird, professor of surgery in the University of London, will deliver the Dr. John Burns Lecture on "Lymphoedema" in the Hall of the Faculty (242, St. Vincent Street, Glasgow) on Wednesday, November 29, at 5 p.m. All medical practitioners are invited to attend the lecture.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The Diploma in Obstetrics of the College has been granted to the following successful candidates: G. H. I. Anderson, W. J. R. Anderson, Beryl G. Bailey, R. J. Balfe, A. W. Banks, W. W. Bardiger, P. J. H. Barron, Luise Beer, W. G. M. Bell, S. Blaxland, S. W. Bowden, J. R. Bowker, R. McC. Boyce, Marjorie C. Bremner, J. H. Brenner, A. T. Bromley, Kathleen A. S. Brosnan, M. L. Bynoe, Irene F. Callender, K. A. A. Campbell, G. A. Carnachan, Maldwyn L. Cattell, N. P. Chaliha, Helen Li-Chu Chang, D. Charles, C. R. Cheadle, C. C. Clapham, Gwen S. Clark, Helen A. Clark, Jean Cockburn, Mary P. Cole, R. N. O. G. Colley, M. B. Comerford, J. M. Crossley, C. A. Cussen, C. N. D'Arcy, Sheila P. Davidson, W. M. Davies, T. R. Davison, L. K. Dawson, Elizabeth A. De Costres, Mary Dixon, D. J. Dooley, E. R. Dunn, W. E. B. Edge, M. Ellue, R. G. Emerson, Margaret T. England, K. A. Exley, Mary A. Foley, Joan Ford, T. A. Frewin, Kathleen M. Frith, Margaret Garnett, Marianne T. Gaston, J. M. Gate, B. A. Gavourin, K. K. Ghosal, Gladys M. B. Gill, N. G. Glen, Wendy E. Greengross, S. Hamilton, J. A. R. Hanna, L. M. Harrison, Geraldine Hector, Agnes B. Johnstone, G. F. Jolly, D. A. Ll. Jones, Shireen Kazi, Gwenyth H. Kendrick, Sylvia Kershaw, Marjorie A. C. Kuck, Margaret A. Lakeman, Tamsin M. R. Lee, Margaret B. Lees, N. Lees, D. G. A. Leggett, G. A. Lewis, J. W. Lewis, Lilias H. Liston, S. E. Lyle, B. Lytton, L. McEntee, M. B. McEvedy, Mary L. Macfarlane, W. J. McKimmon, I. Macpherson, J. M. S. Manson, D. N. Menzies, J. Meyrick, M. W. Mills, R. G. Milne, S. Munir, T. J. M. Myles, S. K. Nag, P. D. Nathan, P. Nayar, R. G. Nell, P. Nirula, A. M. O'Driscoll, J. J. Owies, T. C. L. Parry, S. M. Phadke, W. R. Plews, Rosabelle J. B. Purves, W. L. G. Quinlivan, R. J. Rabett, D. Razzak, N. A. Regan, Frances M. Richards, Joan A. Robertson, D. Rossdale, R. K. Rowntree, M. H. Russell, T. J. Ryan, M. S. Sanders, D. E. Sargent, R. Sathiah, D. Scander, J. S. Scott, G. M. F. Seelig, S. K. Sharma, Esme J. Simpson, P. S. Sinclair, J. A. Smith, Jean P. Spalding, A. D. Stewart, Mary L. Stokes, P. K. Storah, J. M. Stuart, W. H. Tandy, Joyce K. Tate, N. A. Thomas, W. M. Thomas, C. H. Thomson, J. V. Thurston, Rita D. C. Tozer, J. H. S. Wakelin, Ellen Watkinson, D. J. White, P. P. Wium, Wanda H. Wodzinska, G. E. Wolffe, D. J. Woodford, Ma Hnin Yi.

No. 44

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended November 4.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each Infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1950 (a)	1950 (b)	1950 (c)	1950 (d)	1950 (e)	1949 (Corresponding Week) (a)	1949 (Corresponding Week) (b)	1949 (Corresponding Week) (c)	1949 (Corresponding Week) (d)	1949 (Corresponding Week) (e)
Meningococcal infection	32	2	11	1	1	18	2	20	2	1
Deaths		2	1				—	—		
Diphtheria	49	5	18	5	4	86	8	34	4	2
Deaths	—	—	—	—	—	—	—	—	—	—
Dysentery	260	16	124		—	83	2	70	1	3
Deaths		—			—				—	—
Encephalitis, acute	8	1	—		—	1	—	—	—	—
Deaths		—		—			—			
Erysipelas			29	4	4			29	12	8
Deaths							—			
Infective enteritis or diarrhoea under 2 years				25	18				64	
Deaths	6		3	1	—	29	2	5	14	4
Measles*	7,815	512	131	119	71	1,082	33	32	80	68
Deaths†		—	1	—	—			—	—	—
Ophthalmia neonatorum	35	2	10		1	35	4	4	—	—
Deaths										
Paratyphoid fever	5	—	—		—	7	—	2(B)	—	1(B)
Deaths	—		—		—	—	—	—	—	—
Pneumonia, influenzal	433	30	6		7	419	21	3	1	5
Deaths (from influenza)‡	19	4	—	1	—	17	2	2	—	—
Pneumonia, primary			137	¶				179	24	
Deaths	200	24		3	11	197	38		7	8
Poliomyelitis, acute	204	12	18	2	9	330	50	3	4	5
Deaths§	19	1		—		35	5			
Puerperal fever			5				—	15		
Deaths										
Puerperal pyrexia‖	59	5	5	1	3	65	8	5	1	3
Deaths							—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,108	82	193	70	63	2,048	161	269	162	174
Deaths†		—	—	—	—			—	1	—
Smallpox	—	—	—		—	1	—	—	—	—
Deaths					—				—	—
Typhoid fever	—	—	2	6	2	11	—	—	—	—
Deaths	—	—	—		—	1	—	—	—	—
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths					—				—	—
Whooping-cough	3,087	305	409	35	25	898	26	51	35	38
Deaths	4	—	—	—	—	2	—	1	—	1
Deaths (0–1 year)	191	21	34	13	13	249	30	34	30	12
Deaths (excluding stillbirths)	5,025	767	602	134	110	5,309	930	569	180	116
Annual death rate (per 1,000 persons living)			12·1					11·4	11·2	
Live births	6,659	1100	795	369	235	6,912	1103	886	401	213
Annual rate per 1,000 persons living			16·0					17·8	24·8	
Stillbirths	163	17	22			193	19	28		
Rate per 1,000 total births (including stillborn)			27					31		

* Measles is not notifiable in Scotland, and the returns are therefore an approximation only.

† Deaths from measles and scarlet fever for England and Wales, London (administrative county), will no longer be published.

‡ Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

§ The number of deaths from poliomyelitis and polio-encephalitis for England and Wales, London (administrative county), are combined

‖ Includes puerperal fever for England and Wales and Eire.

¶ Primary pneumonia no longer notifiable in Eire.

EPIDEMIOLOGICAL NOTES

Poliomyelitis

Notifications of poliomyelitis in the week ending November 11 were: paralytic, 161 (147); non-paralytic, 64 (57); total, 225 (204). The figures for the previous week, compared with which there was an increase of 21 notifications, are in parentheses. Notifications for the corresponding week in 1947 and 1949 totalled 210 and 316 respectively.

Total uncorrected notifications for 1950 to and including the week under review are 7,972. The corresponding figures for 1947, 1948, and 1949 are 8,475, 2,113, and 5,905 respectively.

Significant increases compared with the preceding week occurred in Cheshire (10), Dorset (10), Durham (6). The more significant decreases were in Warwick (5) and Denbigh (5). In 21 county areas there were no notifications at all.

There was in the week under review a check in the steady decline in notifications of recent weeks. It is unlikely that it is more than a momentary one.

Discussion of Table

In *England and Wales* an increase occurred in the number of notifications of measles 1,183 and dysentery 19, and a decrease was recorded for acute poliomyelitis 49 and scarlet fever 33.

A rise in the incidence of measles was reported from most areas of the country. The largest rises were Yorkshire West Riding 313, Yorkshire East Riding 186, Surrey 159, and Middlesex 116. Only small variations occurred in the local trends of scarlet fever. The notifications of diphtheria were 9 more than in the preceding week; the largest variation was an increase of 5 in Lancashire. The largest fluctuations in the trends of whooping-cough were rises in Middlesex 55, Warwickshire 47, Essex 37, and a fall of 30 in Lancashire.

The chief centres of dysentery were Essex 48 (Leyton M.B. 36); Leicestershire 37 (Leicester C.B. 25); Lancashire 36 (Oldham C.B. 12, Liverpool C.B. 11); Yorkshire West Riding 19; London 16; Gloucestershire 10.

The largest returns of acute poliomyelitis were Yorkshire West Riding 16; Warwickshire 15 (Birmingham C.B. 13); Lancashire 14 (Liverpool C.B. 4); Gloucestershire 13 (Bristol C.B. 11); London 12; Devonshire 10 (Plymouth C.B. 4); Cornwall 10 (Fowey M.B. 4).

In *Scotland* increases of 102 in the number of notifications of whooping-cough and 22 for acute primary pneumonia were recorded, and there was a decrease for dysentery of 20. The chief centres of dysentery were Glasgow 48, Edinburgh 22, and Lanark county 22. The largest returns for acute poliomyelitis were Glasgow 6 and Dundee 3. A decrease of 10 was reported in the number of notifications of scarlet fever in Glasgow.

In *Eire* decreases occurred in the number of notifications of whooping-cough 47, scarlet fever 17, and diarrhoea and enteritis 15, and an increase of 24 was reported for measles. The trends of these diseases were common to the country as a whole. The six cases of typhoid were notified as isolated cases throughout the country.

In *Northern Ireland* a decrease of 27 in the number of notifications of measles and a rise of 15 for scarlet fever were the largest variations in the trends of infectious diseases. The notifications of acute poliomyelitis increased to 9. The largest returns were Londonderry county 3 and Down county 2.

Week Ending November 11

The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,206, whooping-cough 3,725, diphtheria 55, measles 8,857, acute pneumonia 465, acute poliomyelitis 225, dysentery 411, paratyphoid fever 3, and typhoid fever 3.

The Ministry of Health issued a list of amendments to the National Health Service Hospitals Directory on November 13.

Medical News

Royal Society Medallists

Royal medals for the current year are being awarded to Sir Edward Appleton for his work on the transmission of electromagnetic waves round the earth and for his investigations of the ionic state of the upper atmosphere; and to Dr. C. F. A. Pantin for his contributions to the comparative physiology of the invertebrata, particularly his work on nerve conduction in crustacea and actinozoa. The Copley Medal goes to Sir James Chadwick for his outstanding work in nuclear physics and in the development of atomic energy, especially for his discovery of the neutron; the Rumford Medal to Air Commodore Sir Frank Whittle for his pioneering contributions to the jet propulsion of aircraft; the Davy Medal to Sir John Simonsen for his distinguished researches on the constitution of natural products, especially the plant hydrocarbons and their derivatives; the Darwin Medal to Professor F. E. Fritsch for his distinguished contributions to the study of algology; and the Hughes Medal to Professor M. Born for his contributions to theoretical physics in general and to the development of quantum mechanics in particular.

Central Midwives Board

At a meeting on November 2 the Board placed on record its high appreciation of the services rendered by Professor F. S. Langmead, M.D., F.R.C.P., during his five years as representative of the Royal College of Physicians on the Board, and the chairman extended a welcome to Professor A. A. Moncrieff, M.D., F.R.C.P., who succeeds him.

Calls to the Bar

C. W. Robertson, M.B., Ch.B. (Inner Temple), and H. G. Broadbridge, M.B., B.S. (Middle Temple), were called to the Bar on November 17.

Portsmouth and I.o.W. Area Pathological Service

The central laboratory of the Portsmouth and Isle of Wight Area Pathological Service, which serves all the hospitals and general practitioners in the region, was opened by Countess Mountbatten of Burma on November 13.

Child Psychiatry: International Course in London

Some 30 psychiatrists, paediatricians, and social workers from 19 countries in Europe, the Middle East, and Latin America began a course on child psychiatry in London on November 12. The programme has been arranged by the British Council, with Dr. Kenneth Soddy and Dr. Emanuel Miller as advisers. It extends over three weeks and forms part of a comprehensive "Cours de Psychiatrie Sociale de l'Enfant" arranged by the Centre International de l'Enfance between October 15 and December 15. The first part has already been held in Paris, where the Centre's headquarters are situated.

Care and Rehabilitation of Tuberculous Persons

The London County Council has sought the advice of the Minister of Health on dealing with persons suffering from tuberculosis and still infectious, but unlikely to receive further benefit from sanatorium treatment, and without a home or having home conditions which are unsuitable. The Minister is not able to accept the council's view that the provision of hostels for such persons is the responsibility of the regional hospital boards. He contemplates the provision of hostels and night sanatoriums by local health authorities as part of the future development of the tuberculosis services, but in view of present national circumstances he does not feel that this development, among others no less necessary to meet acute problems, should be proceeded with as yet. The council, however, while appreciating these considerations, believes that the problem is so urgent that some contribution should be made towards its solution now. It is to seek approval by the Minister for provision by the council of hostel accommodation if this can be

done by utilizing money voted for other Health Service purposes but which would not be spent immediately. It sees the prospect of meeting one project on these lines during the current financial year.

Tuberculosis Prize

The N.A.P.T. is offering a 100-guinea prize for the best essay embodying the author's ideas and proposals for the improvement of the control of tuberculosis throughout Britain. The competition is open to doctors of ten years' standing who are working as tuberculosis officers, chest physicians, or sanatorium medical superintendents in the United Kingdom. Opinions should be based on personal experiences, and special regard will be paid to the originality of the views expressed. The competition is open until March 1, 1951, and further details can be obtained from the secretary-general, N.A.P.T., Tavistock House North, Tavistock Square, London, W.C.1.

Devon and Exeter Medico-chirurgical Society

At a meeting on October 26, Mr. George Alexander, F.R.C.S., director of the neurosurgical unit, Bristol University, talked on the increasing scope of neurosurgery. Surveying aspects of the whole field in turn, he said that the pain of trigeminal neuralgia is one amenable to surgery, and that, while the results of chordotomy and of posterior root section for painful phantom limb are apt to be disappointing, hammering the stump gives better results. Spinal tumour may masquerade as disseminated sclerosis, and should be suspected if the lesion is progressive. Spontaneous subarachnoid haemorrhage due to rupture of a congenital aneurysm often demands surgical interference, especially in young adults, and certain cases of spina bifida, of hydrocephalus, and of essential hypertension can also be helped. Of head injuries only that minority which show regressive symptoms require surgery.

Diabetes Lecturer for the Netherlands

Dr. R. D. Lawrence, physician-in-charge of the diabetic clinic, King's College Hospital, is visiting Amsterdam, Rotterdam, Leyden, and Utrecht from November 19 to 26 to lecture on recent developments in the treatment of diabetes.

New Journals

The American Academy of Neurology is to produce a new journal, *Neurology*, bimonthly to cover every aspect of clinical neurology, including diseases of the nervous system, neuropathology, and neuropsychiatry. The first issue will be in January, 1951. The new journal is being published on behalf of the Academy by Lancet Publications, Inc., Minneapolis, publishers of the *Journal-Lancet* (now in its eighty-first year), *Modern Medicine* (18 years old), and *Geriatrics*.

The *International Dental Journal*, which has recently made its appearance, is sponsored by the International Dental Federation. At present it appears in an English edition only, with summaries and news items in French, German, Italian, and Spanish. As soon as practicable the journal will be published in full in each of these languages. It is distributed in this country by Cassell and Co. and will appear quarterly, at an annual subscription of £2 5s.

From Japan we have received the first two issues (January and June, 1950) of the *Annals of Tuberculosis*. This is published in English, from the Research Institute for Tuberculosis, Tenri, Nara, Japan.

Italian Medical Film Unit

The Mario Donati Foundation for medical and surgical research has instituted a film section of the Istituto Cinematografico Educativo Scientifico (Educational and Scientific Film Institute). Its aims are to disseminate knowledge of medical and scientific films. The section will catalogue all Italian medical films, covering existing as well as new ones; organize a medical film library to be kept at the disposition of Italian and foreign scientific centres; communicate with similar foreign institutions; and organize national and international shows of medical films. The section will have its office at the Mario Donati Foundation, 6, Via S. Andrea, Milan.

Wills

Dr. William Campbell Elliott Diamond, of Gateshead, formerly of the Malayan Medical Service, left £4,472. Lieut.-Col. Francis James Palmer, R.A.M.C., of Boscombe East, left £19,358. Dr. John Edward Lovelock, the former Olympic champion, assistant director of physical medicine and director of rehabilitation at the Manhattan Hospital for Special Surgery in New York, left estate in England valued at £7,512. Major Francis Aidan Robinson, R.A.M.C.(ret.), of Dringhouses, left £22,690. Professor Charles Stanley Gibson, of Kingswood, Surrey, emeritus professor of chemistry in the University of London at Guy's Hospital Medical School, left £24,251. Col. Alfred Henry Proctor, I.M.S.(ret.), of Hexham, dean of the British Postgraduate Medical School for the first ten years of its existence, left £15,541. Mr. Robert Devereux Mothersole, of Heaton, Bolton, a former chairman of the Bolton Division of the British Medical Association and president of the Lancashire and Cheshire Branch, left £11,997.

COMING EVENTS

Osler Club

The next meeting of the Osler Club will be held on Friday, December 1, at 8 p.m., at the Medical Society of London, 11, Chandos Street, W. Professor Sir Sydney Smith will give an address on the history and development of forensic medicine.

Harben Lectures

Sir Leonard Parsons, F.R.S., emeritus professor of paediatrics and child health and dean of the faculty of medicine in the University of Birmingham, will deliver the Harben Lectures for 1950 on "Studies on Child Health" at the Royal Institute of Public Health and Hygiene, 28, Portland Place, London, W., on Monday, Tuesday, and Wednesday, December 11, 12, and 13, at 4.30 p.m. In the first lecture Sir Leonard Parsons will discuss "Historical Background: The Unborn Child"; in the second, "The Newborn Child and the Infant"; and in the last lecture, "The Older Child: a Glance into the Future." The lectures are open to all medical practitioners and medical students. Admission is free, without ticket.

Congress on Tuberculosis, Uruguay

The Fourth Uruguayan Congress on Tuberculosis will take place in Montevideo on December 11 and 12. Topics for discussion will include the treatment of tuberculosis by antibiotics, and practical experience of mass radiography in Uruguay. The address of the secretariat of the Congress is: Casilla de Correo 2605, Zona 2, Montevideo, Uruguay.

Thomas Vicary Lecture

Mr. William Doolin will deliver the Thomas Vicary Lecture before the Royal College of Surgeons of England (Lincoln's Inn Fields, London, W.C.) on Wednesday, December 13, at 4 p.m. His subject is "Dublin's Surgeon-Anatomists."

Association of Sea and Air Port Health Authorities

A meeting of the Association of Sea and Air Port Health Authorities will be held at the London School of Hygiene and Tropical Medicine, Keppel Street, Gower Street, W.C., on Wednesday, December 13, at 11.45 a.m. A meeting of the medical committee of the association will be held at 10.30 a.m., and a visit to London Airport at 2 p.m. is being arranged.

Wilkins Lecture

Professor F. J. Cole, F.R.S., will deliver the Wilkins Lecture on "The History of Micro-dissection" before the Royal Society (Burlington House, Piccadilly, London, W.) on Thursday, December 14, at 4.30 p.m.

Medical Society of London

The annual oration will be delivered before the Medical Society of London (11, Chandos Street, Cavendish Square, W.) by Sir Charles Symonds on Monday, May 7, at 8.45 p.m.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday

●INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, London, W.C.—November 27, 5 p.m., *"Basal Ganglia Syndromes,"* by Dr. J. St. C. Elkington.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—November 27, 5.30 p.m., *"The External Rhinostomies,"* by Mr. B. W. Rycroft.

MEDICAL SOCIETY OF LONDON, 11, Chandos Street, Cavendish Square, W.—November 27, 8.30 p.m., *"Maintenance of Fluid Balance,"* discussion to be introduced by Dr. H. L. Marriott and Dr. N. R. Lawrie.

●ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 27, 5.30 p.m., *"Anatomy of the Eye and Orbit,"* by Professor T. Nicol.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—November 27, 4.45 p.m., *"Aspects of Protein Structure,"* by Dr. A. Elliott and Dr. W. E. Hanby.

Tuesday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., November 28, 5.30 p.m., *"Blood and Bile Pigments,"* by Professor C. Rimington, Ph.D., D.Sc.

EDINBURGH POSTGRADUATE BOARD FOR MEDICINE.—At University New Buildings (Anatomy Lecture Theatre), Edinburgh, November 28, 5 p.m., *"The Normal Heart,"* by Professor Crighton Bramwell.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 28, 5 p.m., *"Pathology,"* by Dr. J. O. Oliver.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—(1) At St. Paul's Hospital, Henrietta Street, London, W.C., November 28, 11 a.m., *"V.D. in Relation to Pregnancy,"* by Dr. W. N. Mascall; (2) at St. Peter's Hospital, Henrietta Street, London, W.C., November 28, 3 p.m., ward round by Mr. Harland Rees; (3) at St. Paul's Hospital, Henrietta Street, London, W.C., November 28, 5 p.m., *"Gonococcal Urethritis,"* by Dr. W. N. Mascall.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 28, 5 p.m., *"Science and Art of Refraction,"* by Dr. T. H. Whittington.

Wednesday

EDINBURGH CLINICAL CLUB.—At Westerlea School for Spastic Children, Ellersley Road, Murrayfield, November 29, 4 p.m., clinical meeting by Mr. G. A. Pollock.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 29, 5 p.m., *"Medical Mycology,"* lecture-demonstration by Dr. R. W. Riddell.

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—November 29, 5.30 p.m., *"Recent Advances in Ocular Therapeutics,"* by Mr. H. Ridley.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—At St. Paul's Hospital, Henrietta Street, London, W.C., November 29, (1) 11 a.m., *"Urethritis of Non-venereal Origin,"* by Dr. A. H. Harkness; (2) 3.30 p.m., *"X-rays,"* by Mr. J. G. Sandrey; (3) 5 p.m., *"Non-gonococcal Urethritis,"* by Dr. A. H. Harkness.

NORTH-EAST LONDON CLINICAL SOCIETY.—At Prince of Wales's General Hospital, Tottenham, London, N., November 29, 8.15 p.m., *"Some Medical Accidents,"* by Dr. C. Alan Birch.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 29, 3.45 p.m., *"The Application of Biochemistry to Clinical Problems,"* by Dr. N. Martin.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 29, 4 p.m., *"Clinical Ophthalmology"* (Revision), by Mr. R. A. Burn and Mr. R. P. Crick; 5.30 p.m., *"Ophthalmic Neurology,"* by Mr. L. H. Savin.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW, 242, St. Vincent Street, Glasgow.—November 29, 5 p.m., *"Lymphoedema,"* Dr. John Burns Lecture by Professor Ian Aird.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, London, W.—November 29, 3.30 p.m., *"The Work of the Greater London Blood Transfusion Service,"* by Major A. W. Pilgrim, F.C.I.S.

ROYAL SOCIETY OF ARTS, John Adam Street, Adelphi, London, W.C.—November 29, 2.30 p.m., *"Cities Without Noise,"* by Lord Horder.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—November 29, 5.30 p.m., *"Postwar Physics,"* inaugural lecture by Professor H. S. W. Massey.

Thursday

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, Keppel Street, London, W.C., November 30, 5.30 p.m., *"The Mechanism of Hypertension,"* by Professor G. W. Pickering.

HONYMAN GILLESPIE LECTURE.—At University New Buildings (Anatomy Theatre), Teviot Place, Edinburgh, November 30, 5 p.m., *"Colonic Pain and the Colon Neurosis,"* by Dr. Charles M. Seward.

●INSTITUTE OF DERMATOLOGY, Lisle Street, Leicester Square, London, W.C.—November 30, 5 p.m., *"Diseases Caused or Aggravated by Light,"* by Dr. B. Russell.

INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, London, S.E.—November 30, 3 p.m., *"The Frontal Lobe,"* by Professor A. Meyer.

INSTITUTE OF UROLOGY (UNIVERSITY OF LONDON).—At St. Paul's Hospital, Henrietta Street, London, W.C., November 30, (1) 11 a.m., *"Sociological Problems of V.D.,"* by Dr. R. Lees; (2) 5 p.m., *"Diseases of the Female Urethra,"* by Mr. H. G. Hanley.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool.—November 30, 8 p.m., *"Tracer and Therapeutic Studies with Radio-isotopes,"* by Mr. R. Marcus.

LONDON UNIVERSITY, Senate House, Bloomsbury, W.C.—November 30, 5.30 p.m., *"The Biological Aspects of War: Consequences,"* by Professor F. A. E. Crew, F.R.S.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 30, 3.45 p.m., *"The Control of Secretions of the Alimentary Tract,"* by Professor W. R. Spurrell.

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—November 30, 5.30 p.m., *"Simple Stricture of the Oesophagus,"* by Professor G. Grey Turner.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—November 30, 5.30 p.m., *"Extraocular Signs and Symptoms of Disease of the Central Nervous System,"* by Dr. T. Rowland Hill.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, Hyde Park Corner, London, S.W.—November 30, 4.30 p.m., lecture-demonstration on neurology, by Dr. A. Feiling.

Friday

INSTITUTE OF OPHTHALMOLOGY, Judd Street, London, W.C.—December 1, 5.30 p.m., *"Ophthalmological Manifestations of Cerebral Atrophy,"* by Dr. Helen Dimsdale.

●MAIDA VALE HOSPITAL MEDICAL SCHOOL, London, W.—December 1, 5 p.m., clinical neurological demonstration by Dr. Douglas McAlpine.

NORTH-WEST METROPOLITAN REGION MENTAL DEFICIENCY SOCIETY.—At Leavesden Hospital, Abbots Langley, Watford, Herts. December 1, films of clinical types and abnormal movements, to be followed by discussion.

●ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, London, W.C.—December 1, 3.45 p.m., *"Some Aspects of the Renal Excretion of Water,"* by Professor E. B. Verney.

ROYAL EYE HOSPITAL, St. George's Circus, Southwark, London, S.E.—December 1, 4.15 p.m., *"Pathology,"* by Miss M. Savory.

●ROYAL INSTITUTION, 21, Albemarle Street, London, W.—December 1, 9 p.m., *"Thought Transference and Related Phenomena,"* by Mr. R. H. Thouless, Ph.D.

ROYAL MEDICAL SOCIETY, 7, Melbourne Place, Edinburgh.—December 1, 8 p.m., *"Erythema Nodosum and Allergy,"* dissertation by Mr. A. J. Keay.

UNIVERSITY COLLEGE, Gower Street, London, W.C.—December 1, 5.15 p.m., *"Chemical Transmitters,"* by Dr. W. S. Feldberg, F.R.S.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—*Consultant Ear, Nose, and Throat Surgeon in Norwich Area*, I. S. Young, M.B., Ch.B., F.R.C.S.Ed., D.L.O. *Anaesthetic Registrar at East Suffolk and Ipswich Hospital*, Miss E. Ruth S. Armitage, M.B., B.S.

RANGER, D., M.B., B.S., F.R.C.S., Assistant Consultant Ear, Nose, and Throat Surgeon, Middlesex Hospital, London, W.

WILSON, B. D. R., M.B., M.R.C.P., Consultant Paediatrician, St. Andrew's Hospital, Bow, London, E.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bolton.—On November 9, 1950, at Bristol Maternity Hospital, to Joyce (formerly Baker), wife of Frederick G. Bolton, M.R.C.P., a son.

Ewing.—On October 31, 1950, at St. Anne's Nursing Home, Oxford, to Evelyn, wife of Richard F. Ewing, M.R.C.S., L.R.C.P., a son—Michael Charles.

Fraser.—On November 8, 1950, to Dr. Mary E. Fraser (formerly Chalmers), wife of R. J. A. Fraser, F.R.C.S.Ed., 77, Anderson Drive, Aberdeen, a daughter.

Todd.—On November 8, 1950, at Edgware General Hospital, to Olive (formerly Gray), wife of K. R. Todd, M.B., B.S., a daughter.

DEATHS

Carling.—On November 15, 1950, at West Cottage, Alton, Hants, William Carling, M.B., B.Ch., late of Southsea and East Grinstead, aged 88.

Cooper.—On October 28, 1950, at 134, Landdrost Street, Vryheid, Natal, South Africa, Moses Kuper Cooper, M.B., Ch.B., late of 11, Arden Street, Edinburgh.

Harley.—On November 13, 1950, at 1, Park West, London, W., Thomas William Harley, C.I.E., M.B., B.Ch., Lieutenant-Colonel, I.M.S., retired, aged 73.

Low.—On November 15, 1950, Alexander Low, M.D., LL.D., Emeritus Regius Professor of Anatomy, University of Aberdeen, of 144, Blenheim Place, Aberdeen, aged 82.

Sinclair.—On November 14, 1950, at his home, Neil Frederick Sinclair, F.R.C.S., of 14, Upper Harley Street, London, N.W.

Speirs.—On November 14, 1950, at St. Dunstan's, Melrose, Roxburghshire, Henry Speirs, M.D., F.R.C.S.Ed.

Utidjian.—On November 12, 1950, at his home, 2, Draycott Close, Kenton, Middlesex, Haigouni Dikran Absolom Utidjian, M.D., of London, formerly of Nicosia, Cyprus, aged 59.

Wade.—On November 15, 1950, at 97, Windmill Hill, Enfield, Middlesex, Herbert Wade, M.R.C.S., L.R.C.P., aged 87.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Retraction of the Foreskin

Q.—*What is the present position with regard to the retraction of babies' foreskins? I was taught, and it has been my practice, to retract them within a week or so after birth, and to give instructions to the mother to do so at weekly intervals, at bathtime. By following out this regime, it is rare to get a failure and, if the mother carries out her instructions, to get any further trouble. But recently in your columns—I refer to Dr. Gairdner's article (Journal, 1949, 2, 1433)—the feeling seems to be to leave the foreskin alone. If so, for how long?*

A.—Dr. Douglas Gairdner's article produced conclusive evidence that the prepuce is still developing in the early years of life, and that by 3 years of age 90% of boys will have a retractable foreskin if nothing whatever has been done. The remaining 10% can be dealt with by gentle manipulation. Despite this it will be seen from the question that doubts still exist, and indeed, as correspondence after the appearance of Dr. Gairdner's article showed, emotion rather than reason seems to govern the attitude of many to this problem. The simple answer to the question is to leave the foreskin alone until the age of 3 years. What the strictly scientific outlook perhaps omits to reckon with is the likely family situation during that three years. The matter will be discussed by father among his friends and by mother with the neighbours and relations. Serious effects upon procreational function will be hinted at, and confusing remarks about masturbation, cancer, and venereal disease will certainly be made sooner or later. Since popular views lag so greatly behind even modern discoveries, it is unlikely that on a subject which goes far back in history an attempt to reverse long-continued practice will meet with immediate success. For the sake, therefore, of the peace of mind of the parents (and of the doctor concerned) there is something to be said for some degree of "gentle manipulation" at an earlier age than Dr. Gairdner suggested. There is also the material point that, if nothing is done about the foreskin along such lines, there is a very real chance that someone will be persuaded to perform circumcision. To avoid this greater evil there are many doctors who feel that gentle retraction of some degree in the early days is advisable.

Sterilization of Paraldehyde

Q.—*Paraldehyde is now widely used intramuscularly, perhaps particularly in the treatment of status epilepticus. Some workers use for this purpose the sterile ampoules now being put up by certain drug houses; others use paraldehyde from the non-sterilized stock-bottle, and assert that the occasional abscesses which result are non-infective and due to tissue sclerosis. (a) Is paraldehyde self-sterile? (b) If not, how is it sterilized?*

A.—Paraldehyde behaves somewhat like alcohol, becoming germicidal only when diluted with water. A saturated (10%) solution kills vegetative bacteria rapidly, but if the bacteria are immersed in the pure substance in the dry state they are unaffected. Paraldehyde should therefore certainly not be regarded as self-sterilizing. The method prescribed for its sterilization is autoclaving in sealed tubes.

Hypertensive Encephalopathy

Q.—*What is the immediate treatment of hypertensive encephalopathy, and how may further attacks be prevented?*

A.—Hypertensive encephalopathy may complicate severe hypertension of any aetiology, and is usually attributed to cerebral vascular spasm associated with a transient exacerbation of hypertension.

The attack itself is best treated by strong sedation, a completely sodium-free diet, and the administration of tetraethylammonium bromide or methonium compounds. Tetraethylammonium bromide may be given intravenously in doses of 200–300 mg., administered rather slowly over a period of about three minutes. Pentamethonium iodide (C5) or hexamethonium iodide (C6) may be given intravenously in doses of 30–40 mg. over a period of two minutes. Subcutaneous or intramuscular injections of either C5 or C6 may be given two or three times daily. According to Smirk (*Lancet*, 1950, **2**, 477) the dose may be less if the patient is nursed propped up; in this position the dose need not exceed 15–25 mg. in the initial stages. As a rule, patients acquire tolerance to the drug and large doses may become necessary.

Prophylactic treatment should be designed to lower the blood pressure, and there is a choice of conservative measures (rest and sedatives), a low sodium diet (or the rice diet), thiocyanates, methonium compounds, or lumbo-dorsal sympathectomy. Space forbids a discussion of the relative merits of these measures.

Waxed Paper and Cancer

Q.—*There is a prevalent belief that the use of waxed paper in cooking is associated with the development of cancer. Is there any truth in this theory?*

A.—The commercial preparation of paraffin wax from shale oil is associated with a certain risk of dermatitis and skin cancer, but even workers in the industry do not appear to have a higher incidence of cancer of the alimentary canal than the average population. It seems unlikely, therefore, that the use of waxed paper as a wrapping for puddings involves an increased risk of alimentary cancer.

How to Stop Smoking

Q.—*Can you suggest any cure for smoking?*

A.—To help anyone stop smoking one must first find out why they smoke. Some smoke from habit, some because they have developed a pharmacological craving, while others claim that it is simply and solely a matter of enjoyment. In any case, one thing is necessary—to instil a desire to stop smoking which is greater than the desire to smoke. When the reasons for smoking are entirely psychological this may not be difficult, as a strong financial reason for stopping may be added to the medical ones; when there is also a pharmacological craving it is another matter. In such a case it is probably best for the patient to make a sharp break rather than for him to try to cut down gradually. The desire to smoke will be found to increase rapidly for 24 hours, but it will then begin to fall away, and, if he can refrain from smoking completely, the urgent desire will have largely disappeared within a week. During this period some people find it helpful to carry a packet of cigarettes about with them and to finger them from time to time. The presence of cigarettes in the pocket has a quietening effect and may prevent the panicky rush to the nearest shop which often follows the realization that no cigarettes are immediately to hand. If the habit appears to be impossible to break in this way, injection of nicotine (1/50 gr. subcutaneously—1.3 mg.) or pastilles (1/50 gr.) by mouth may be effective.

Eosinopenia in Cortisone and A.C.T.H. Therapy

Q.—*In reports on the therapeutic effects of cortisone and A.C.T.H. (adrenocorticotrophic hormone), one cannot but observe the association of an eosinopenia with any clinical improvement. What is the significance of this? Is the eosinopenia a factor in the improvement or merely, as it were, a by-product?*

A.—The questioner is correct in associating a production of eosinopenia with clinical improvement in such conditions as rheumatoid arthritis as a result of cortisone or A.C.T.H. therapy. The eosinopenia is not a consequence of the improvement, but the two effects are brought about by the same agent—namely, adrenal glucocorticoids, of which

cortisone is one, and the secretion of which is stimulated by A.C.T.H. In the latter case, eosinopenia is used as a guide to the capacity of the recipient's adrenal cortex to respond to A.C.T.H. Eosinopenia may be found in the absence of a clinical response, and occasionally the reverse appears to be true. The two processes may therefore be regarded as independent "end organ" responses to A.C.T.H.

Halitosis

Q.—*I have a patient, aged 28, who is troubled by his wife's complaints that he suffers from malodorous breath. I can find no local cause for his halitosis. How should this case be investigated? What are the most likely causes of the condition?*

A.—The almost invariable cause of halitosis is some infection in the mouth or respiratory tract. Such diseases as bronchiectasis and lung abscess appear improbable in the present instance; but the teeth should be carefully scrutinized by a dentist and any gingivitis or cavity treated. In many patients chronic infection of the tonsils is responsible, and this can often be convincingly demonstrated by rubbing the tonsil with the finger, which will then yield olfactory proof of the origin of the fetor. Chronic nasal disease, such as atrophic rhinitis or sinusitis, is another possible cause, and these conditions should be excluded.

Herpes Zoster

Q.—*What are the most recent views on the aetiology of herpes zoster? A woman who sustained an accident with bruising of the ribs developed herpes zoster six days later. Is it possible for the injury to have caused the herpes zoster?*

A.—Herpes zoster is due to a virus which is closely related to the virus of chicken-pox, and not infrequently an attack of zoster in an adult follows contact with a case of chicken-pox in a child. Whether or not clinical infection follows such contact will depend on the degree of specific or non-specific resistance at the time of exposure, but there seems little doubt that any previous devitalization of posterior nerve roots (it is the sensory nerve endings that are principally affected) predisposes to an attack. Thus, exposure to cold may precede an ophthalmic zoster, and it is likely that the injury to the ribs sustained by this patient was a factor predisposing to the subsequent attack of herpes zoster. The incubation period is given as 7 to 14 days.

Sterilization of Bed-pans

Q.—*In most hospitals bed-pan sterilizers are now installed of the type in which the bed-pan is first flushed in cold water, then in hot water, sterilization being effected by a jet of live steam. These machines are simple to work and so convenient to the nurses that they demand their installation.*

(a) Are these sterilizers efficient? (b) If not, how should bed-pans be sterilized? (c) Is there any record of an unchipped bed-pan spreading puerperal sepsis in a maternity hospital, or is it ever likely?

A.—(*a*) Conflicting reports on the efficiency of bed-pan sterilizers are to be explained by the existence of several models. A manually operated sterilizer used by a busy nurse may fail because she turns off the steam too quickly: an automatic model in which the application of steam is continued for a regulated period—usually 20 seconds—is dependable, provided, of course, that the steam pressure is as specified by the makers. Such exposure to steam kills all vegetative bacteria, but it does not kill spores.

(*b*) The alternative is immersion in a disinfectant solution, preferably of phenolic type (such as 2% lysol), or boiling.

(*c*) There appears to be no record of puerperal infection having been conveyed by bed-pans, but it could certainly happen, and may well have done so without the cause having been recognized.

Desensitization to Penicillin

Q.—*I have a patient, aged 54, who suffers from asthma and recurrent bronchitis. The administration of penicillin G provokes severe asthmatic attacks. How can I desensitize him to the penicillin?*

A.—O'Donovan and Klorfajn (*Lancet*, 1946, **2**, 444) desensitized a patient by giving doses of 15,000 units of penicillin by mouth four to eight times a day for a fortnight, and others have found this method successful. It is also said to be possible to desensitize by a long course of injections begun with very small doses. An asthmatic might perhaps not react so readily as an otherwise normal subject.

Before embarking on either of these tedious procedures it would be well to determine that the condition is infective and that the responsible organism is penicillin-sensitive, if this has not already been done.

Carbon Dioxide and Asthma

Q.—*Are inhalations of carbon dioxide of value in the treatment of asthma?*

A.—Carbon dioxide inhalations cause hyperventilation of the lungs but do not relieve the bronchospasm. The patient is generally encouraged to over-breathe in the wrong way—i.e., by the accessory muscles of respiration causing over-inflation of the lungs. In addition, when a patient has had severe asthma for a considerable time, the respiratory centre is fatigued and after stimulation with carbon dioxide may cease to function when the stimulus is removed. The aim should rather be to teach the patient to empty his chest by his own activities; simple breathing exercises will teach him to control his expiration, increase the mobility of the chest wall, and help him to relax the over-acting inspiratory muscles. Such exercises are well known to any qualified physiotherapist and are described in the booklet, *Physical Exercises for Asthma*, published by the Asthma Research Council and obtainable from Messrs. H. K. Lewis, price 2s.

NOTES AND COMMENTS

Tetanus Antitoxin.—Mr. J. R. ELLIOTT (London) writes: In "Any Questions?" (November 11, p. 1128) it is stated that a prophylactic dose of tetanus antitoxin should be between 1,000 and 3,000 units. I would like to draw attention to the fact that since July 1 this year the value of the International Unit (1950) has been twice that of the old International Unit (1928) and is now the same as the U.S.A. Unit. Thus the dose of tetanus antitoxin mentioned in all publications earlier than this date should be halved when the new material is ordered. In order to avoid confusion during this transition period, manufacturers are labelling their products with all three methods of notation—for example, "1,500 International Units (1950) in 1 cc. (= 3,000 I.U. (1928) = 1,500 U.S.A. Units)," and I would suggest that all references to this drug should clearly indicate which unit is required until all suppliers have no possible doubts in the matter.

Correction.—Under "Books Received" (November 11, p. 1101) we mistakenly said that Messrs. George Pulman and Sons, Ltd. are the publishers of the book *Der Muskelstoffwechsel des Herzens*, by Dr. H. Schumann. The only publishers are Verlag von Dr. Dietrich Steinkopff, Darmstadt.

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